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Scheiflinger et al.

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(54) **TREATMENT OF COAGULATION DISEASE
BY ADMINISTRATION OF RECOMBINANT
VWF**

(75) Inventors: **Friedrich Scheiflinger**, Vienna (AT);
Peter Turecek, Klosterneuburg (AT);
Bruce Ewenstein, Brookline, MA (US);
Wing Yen Wong, Simi Valley, CA (US);
Tobias M. Suiter, Vienna (AT)

(73) Assignees: **Baxalta Incorporated**, Bannockburn, IL
(US); **Baxalta GmbH**, Glattpark
(Opfikon) (CH)

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A61P 7/02 (2006.01)

A61K 38/37 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 38/36** (2013.01); **A61K 38/37**
(2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Karlheinz R Skowronek

Assistant Examiner — Sergio Coffa

(74) *Attorney, Agent, or Firm* — Morgan Lewis & Bockius LLP

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ABSTRACT

The present invention provides methods of treating coagulation disease, including hemophilia and von Willebrand disease by administering recombinant von Willebrand Factor alone or in combination with Factor VIII.

32 Claims, 23 Drawing Sheets

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FIG. 2A

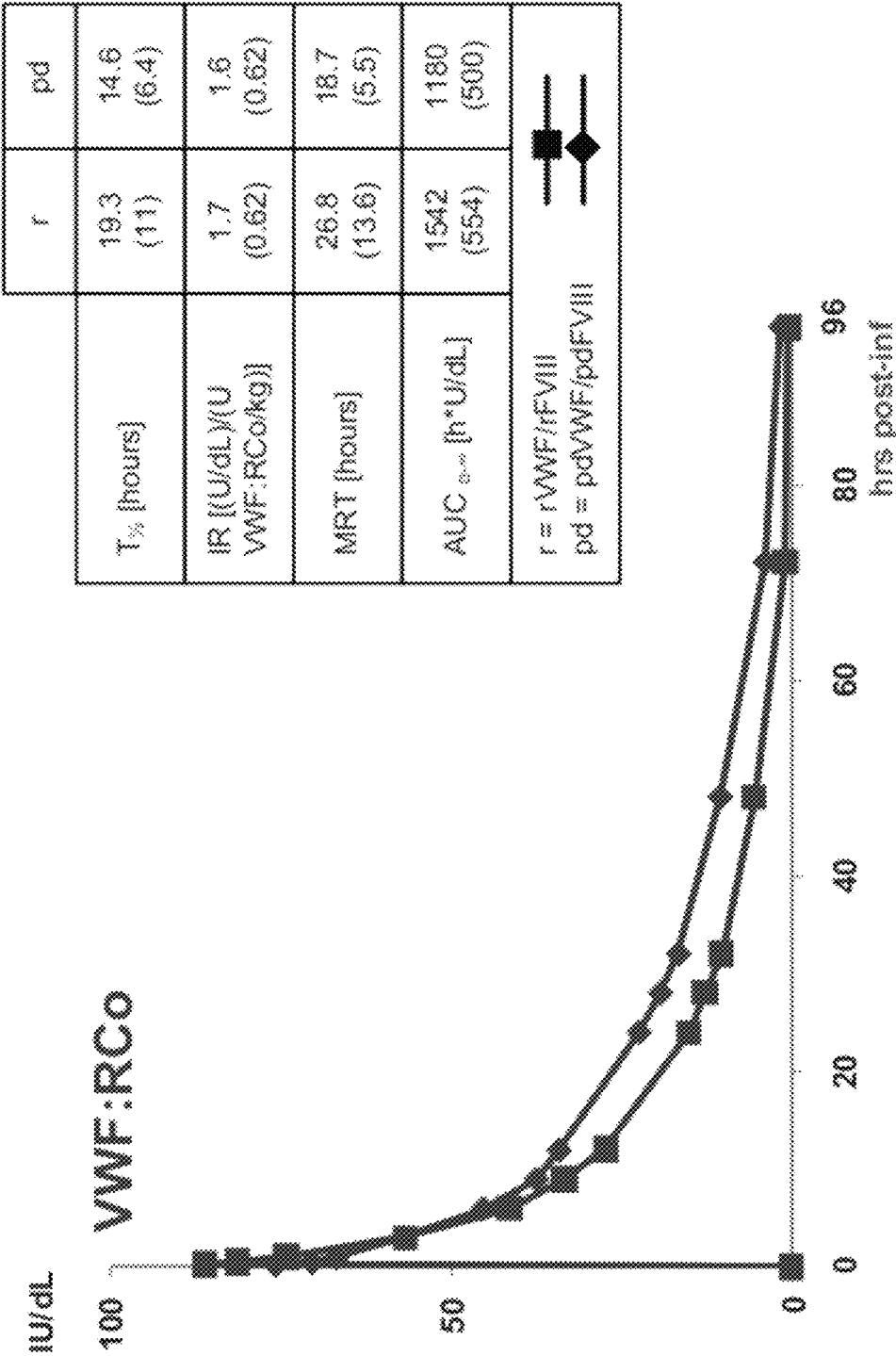


FIG. 2B

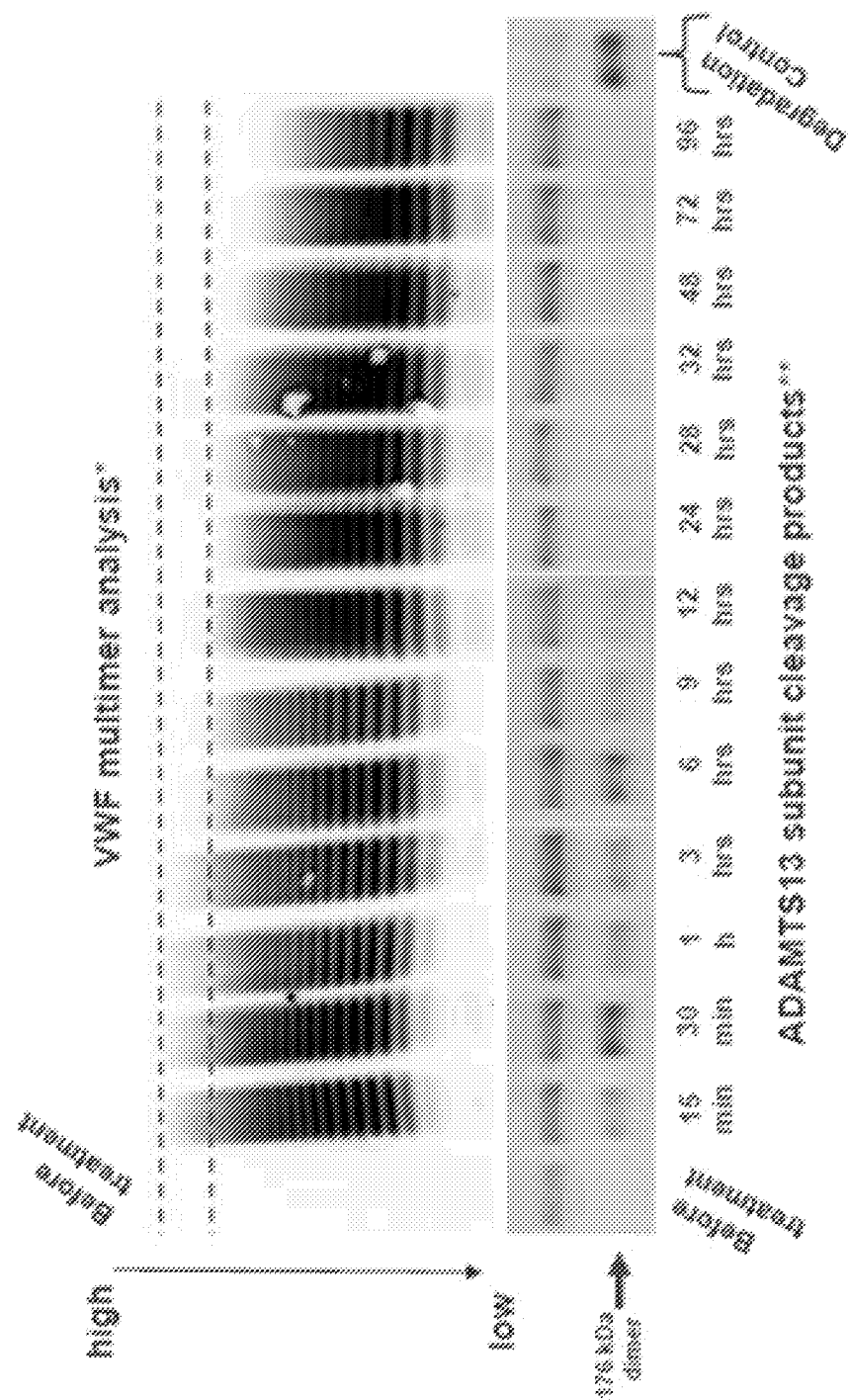


FIG. 3

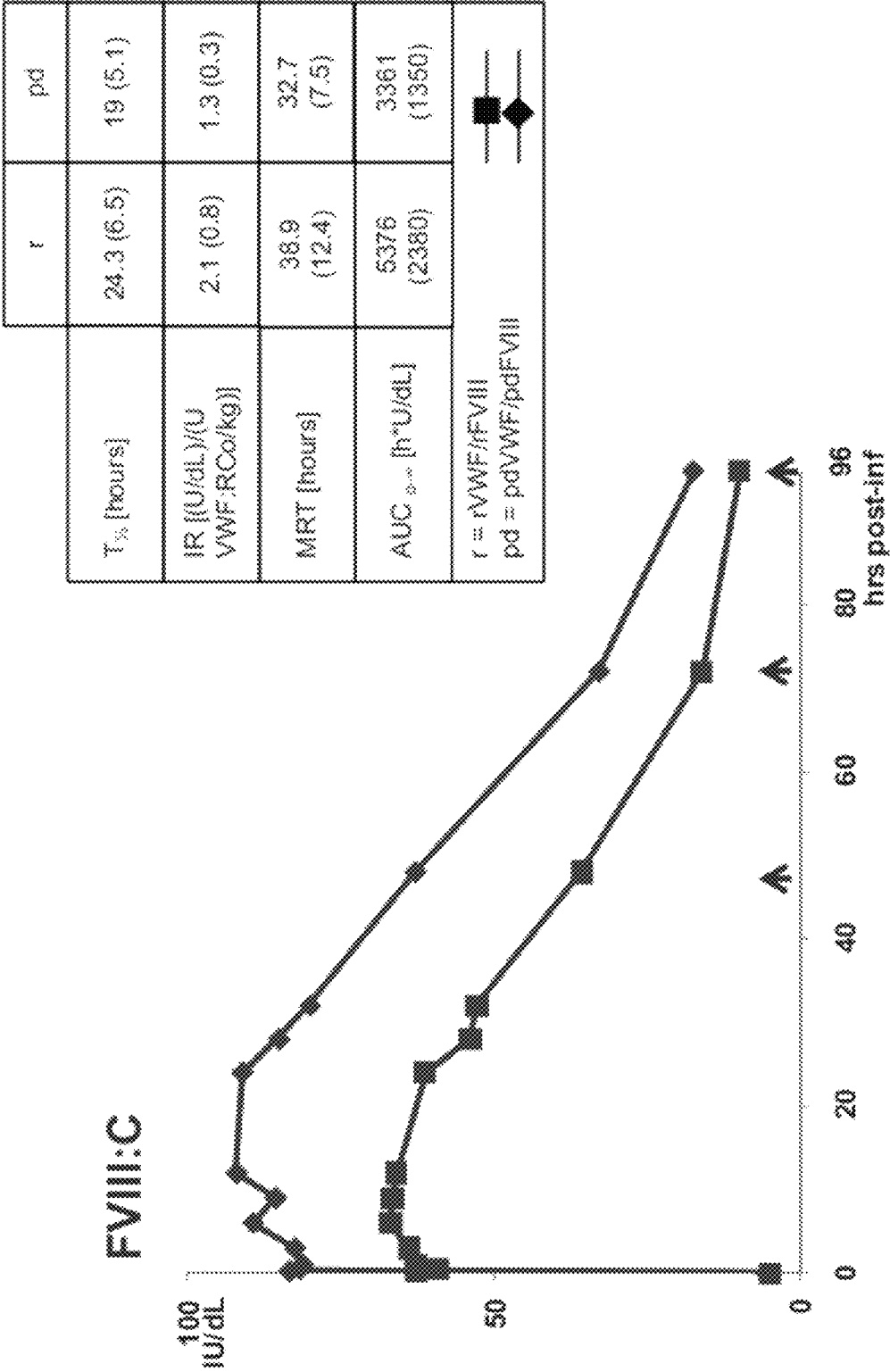
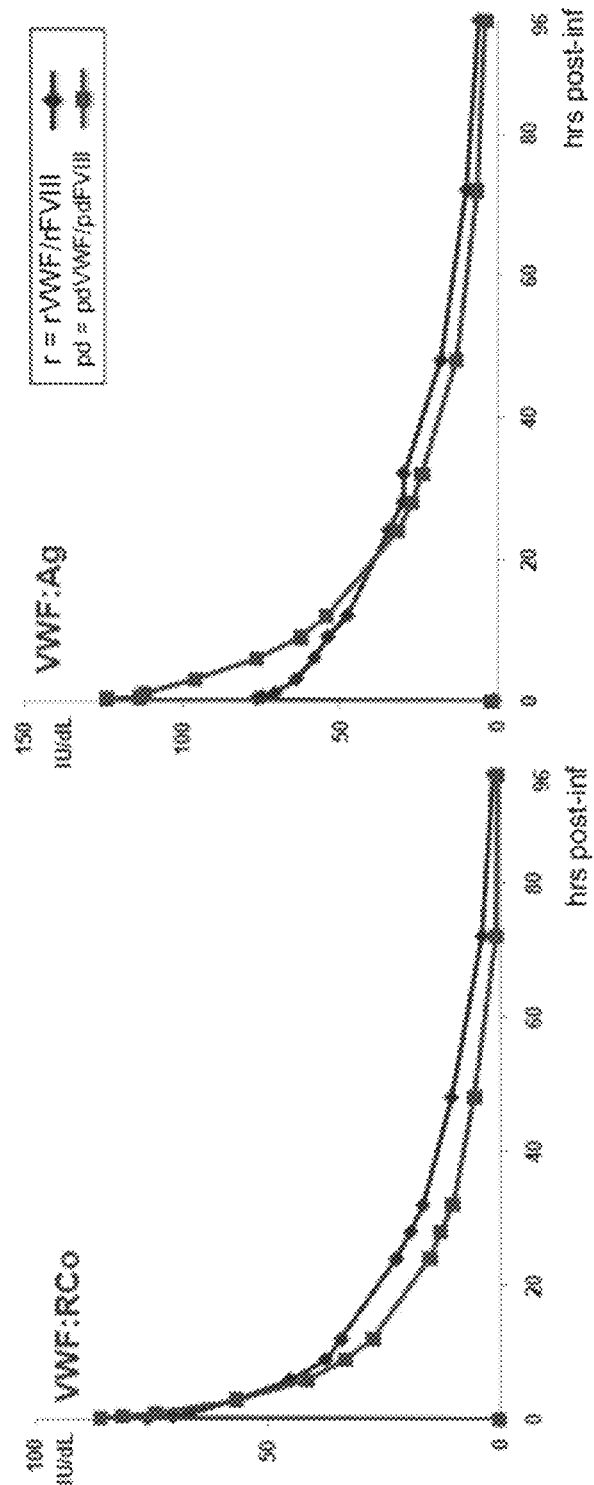


FIG. 4

COHORT	# of patients	Gender (Female/Male)	Age (years) Median (range)	Weight (kg) Median	Ethnicity
1 (Type 3)	3	1/2	38 (26-44)	130	Caucasian
2 (Type 3)	5	2/3	26 (21-39)	86.2	Caucasian
3 (Type 3)	5	0/5	34 (19-55)	79	4 Caucasian 1 Asian
4A (Type 3) (50 IU/kg VWF:RC ₀)	22	11/11	33 (18-60)	74.8	Caucasian
4B (Severe Type 1)	3	2/1	25 (19-47)	82.1	Caucasian
Total	32*	15/17	33 (18-60)	81.1	31 Caucasian 1 Asian

*Six subjects from cohort 1-3 were re-enrolled in cohort 4A

FIG. 5

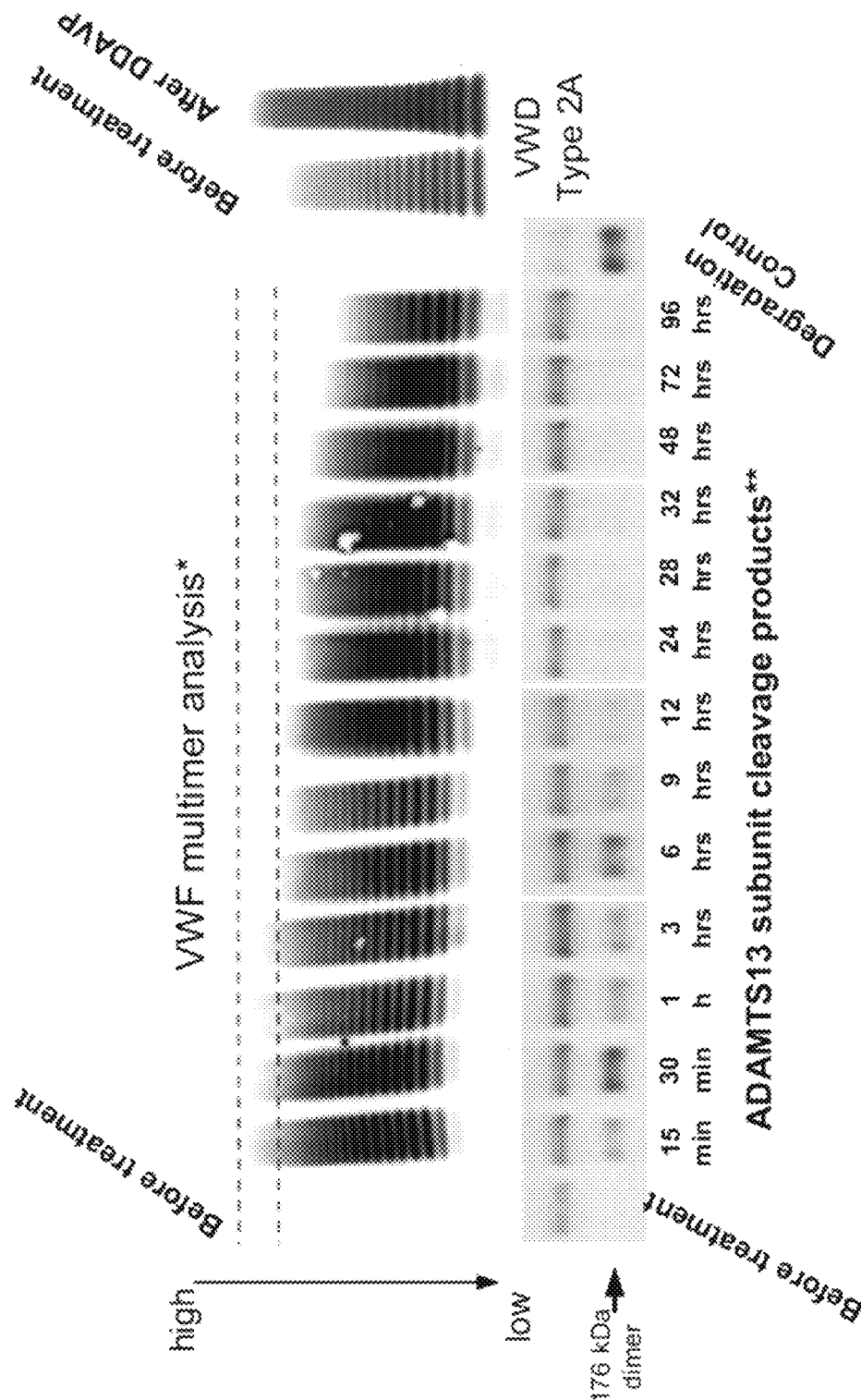


VWF:Ag		r	pd
IR[(U/dL)/(U VWF:RCo/kg)]		1.7 (0.55)	2.3 (0.67)
T _{1/2} [hours]		25.3 (6.3)	18.2 (3.3)
MRT [hours]		33.5 (10.7)	22.4 (5.2)
AUC _{0-∞} [h*U/dL]		2245 (683)	2254 (1012)

VWF:RCo		r	pd
IR[(U/dL)/(U VWF:RCo/kg)]		1.7 (0.62)	1.6 (0.62)
T _{1/2} [hours]		19.3 (10.9)	14.6 (6.4)
MRT [hours]		26.8 (13.6)	18.7 (5.5)
AUC _{0-∞} [h*U/dL]		1542 (554)	1180 (500)

All values are "means"
() Standard Deviation

FIG. 6



*Low resolution agarose (1% Seakem) / Samples adjusted to VWF:Ag content

**SDS-PAGE / Immunoblot with polyclonal anti-VWF Ab / Samples undiluted

FIG. 7

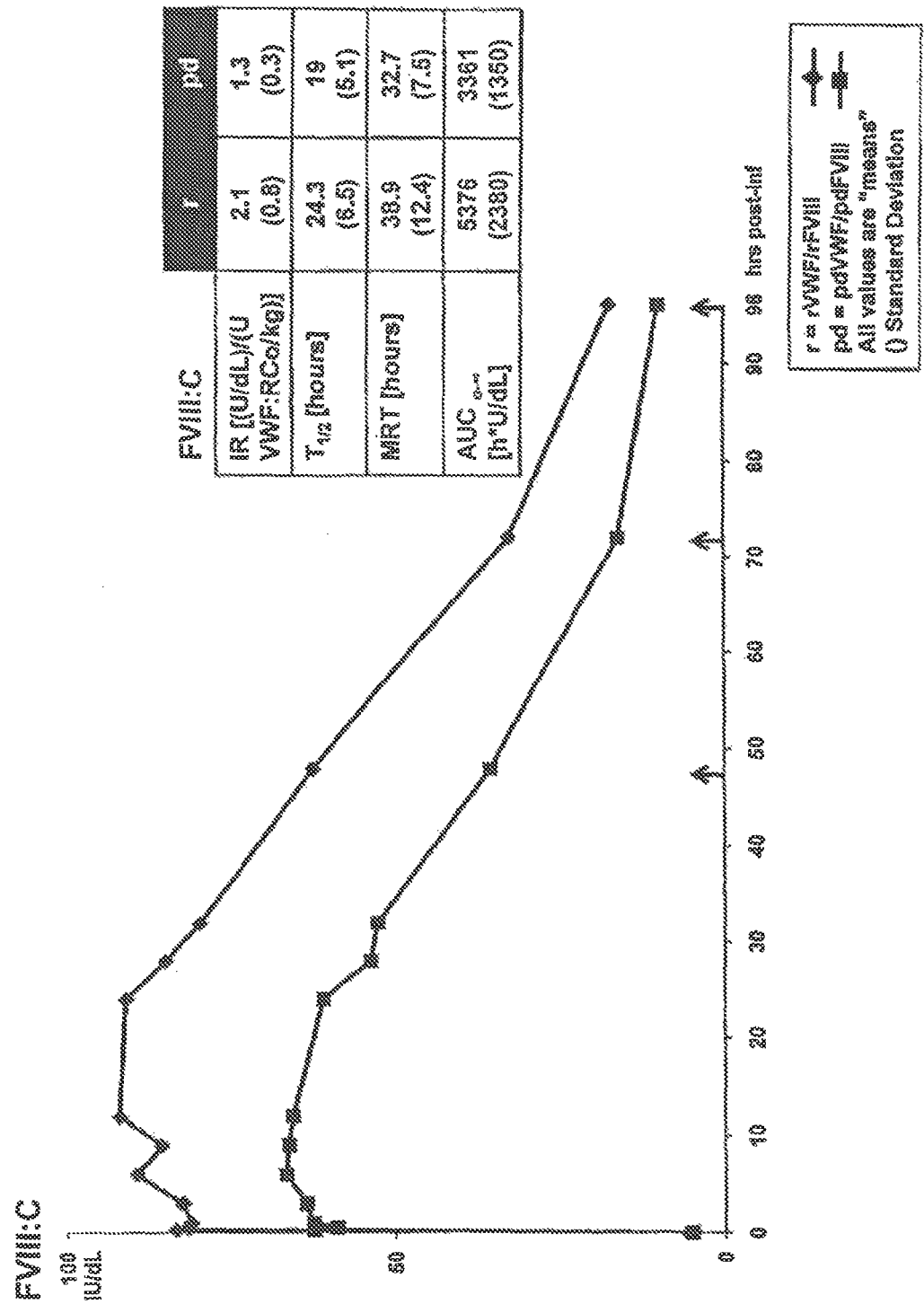


FIG. 8

Cohort	
Cohort 1 (Type 3) n=3	Hypertension**
Cohort 2 (Type 3) n=5	Tremor, generalized pruritus
Cohort 4A (Type 3) n=22	rVWF/rFVIII
	Nausea, sP-selectin increase, dizziness, psychomotor hyperactivity, hypertension**
	pdVWF/pdFVIII
	Low titer anti-VWF Ab, dizziness (n=2), headache

*All reported related adverse events were mild, no related adverse events were reported for cohort 3 and 4B

**Same patient

FIG. 9

Patient 1
02-0001

Time (hours)	VWF:RCo (U/mL)	VWF:Ag (U/mL)	FVIII activity (U/mL)	VWF:CBA (U/mL)
screening	<0.007	<0.01	0.03	<0.01
0	<0.007	<0.01	0.03	<0.01
0.25	0.043	0.05	0.10	0.04
0.5	0.036	0.06	0.08	0.04
1	0.036	0.05	0.09	0.04
3	0.030	0.05	0.11	0.03
6	0.028	0.04	0.13	0.03
9	0.021	0.03	0.13	0.02
12	0.020	0.04	0.13	0.02
24	<0.007	0.03	0.13	<0.01
28	<0.007	0.02	0.12	<0.01
32	<0.007	0.03	0.09	<0.01
48	<0.007	0.02	0.07	<0.01
72	<0.007	0.01	0.05	<0.01
96	<0.007	0.01	0.04	<0.01

Manual Test Baxter Data from the Central Laboratory

Patient 2
02-0002

Time (hours)	VWF:RCo (U/mL)	VWF:Ag (U/mL)	FVIII activity (U/mL)	VWF:CBA (U/mL)
screening	<0.007	<0.01	0.03	<0.01
0	<0.007	<0.01	0.03	<0.01
0.25	0.044	0.04	0.12	0.04
0.5	0.041	0.04	0.13	0.04
1	0.041	0.03	0.14	0.05
3	0.031	0.03	0.16	0.03
6	0.022	0.02	0.18	0.02
9	0.015	0.02	0.16	0.02
12	0.007	0.02	0.14	0.01
24	<0.007	0.01	0.08	<0.01
28	<0.007	0.01	0.09	<0.01
32	<0.007	0.02	0.07	<0.01
48	<0.007	0.01	0.05	<0.01
72	<0.007	0.01	0.03	<0.01
96	<0.007	0.01	0.03	<0.01

Manual Test Baxter Data from the Central Laboratory

Patient 3
07-0001

Time (hours)	VWF:RCo (U/mL)	VWF:Ag (U/mL)	FVIII activity (U/mL)	VWF:CBA (U/mL)
screening	<0.007	<0.01	0.02	<0.01
0	<0.007	<0.01	0.02	<0.01
0.25	0.044	0.05	0.08	0.04
0.5	0.037	0.05	0.09	0.04
1	0.033	0.05	0.09	0.04
3	0.029	0.05	0.11	0.04
6	0.026	0.04	0.13	0.04
9	0.022	0.03	0.12	0.03
12	0.015	0.03	0.12	0.02
24	0.007	0.03	0.04	<0.01
28	<0.007	0.02	0.12	<0.01
32	<0.007	0.02	0.06	<0.01
48	<0.007	0.02	0.06	<0.01
72	<0.007	<0.01	0.04	<0.01
96	<0.007	<0.01	0.02	<0.01

Manual Test Baxter Data from the Central Laboratory

FIG. 10

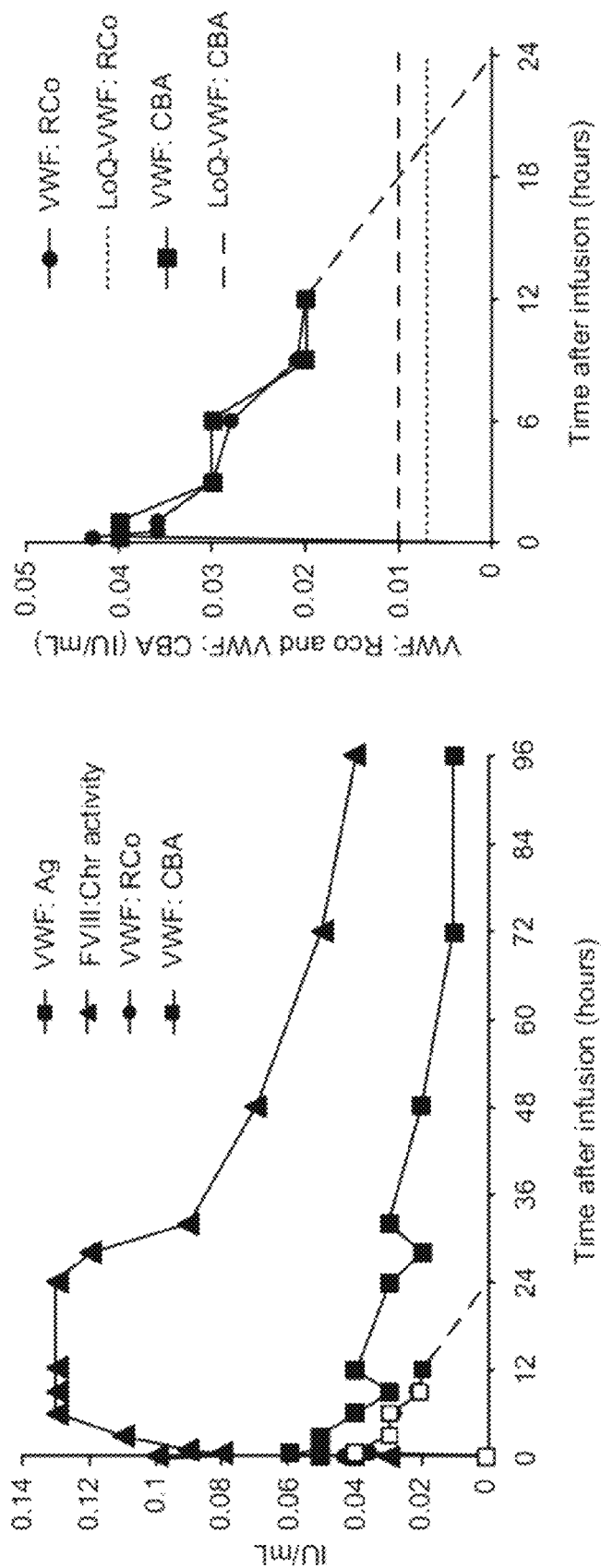


FIG. 11

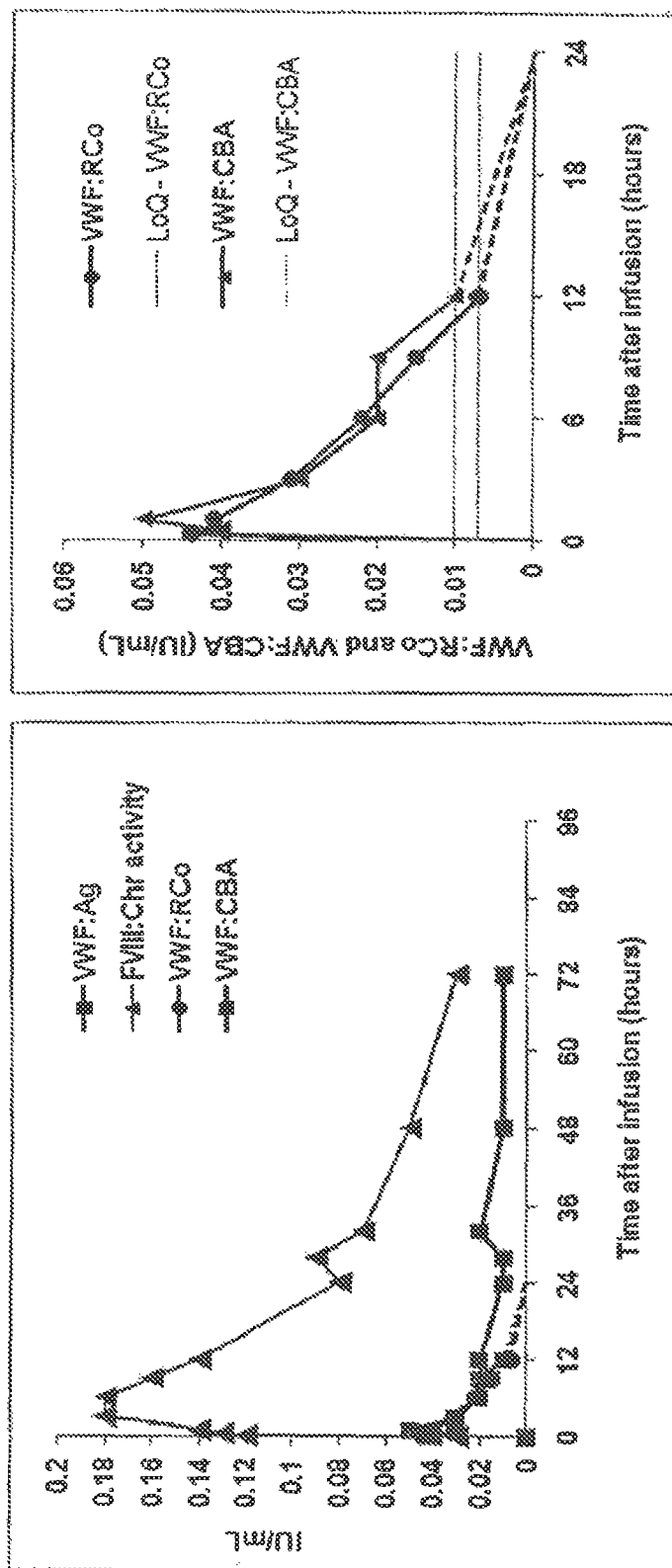


FIG. 12

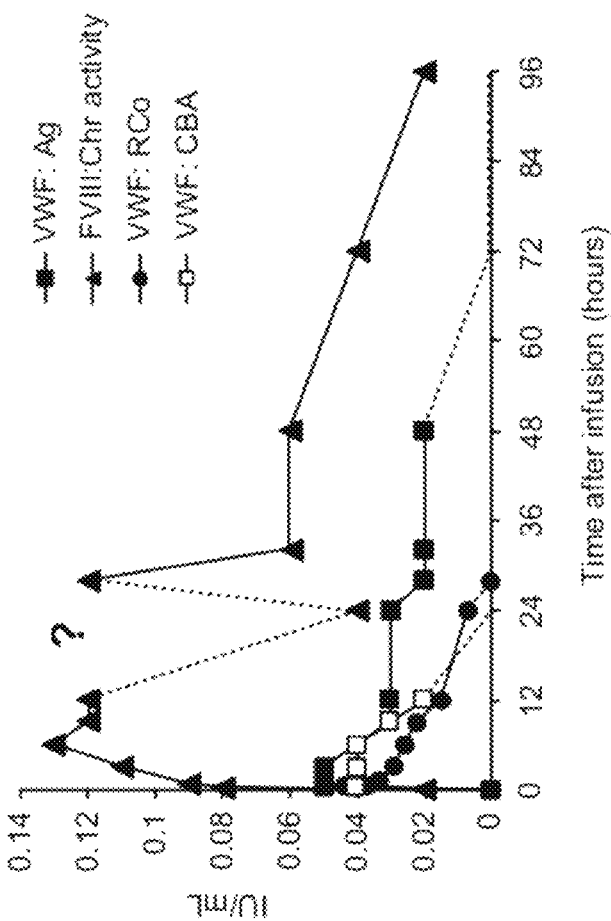
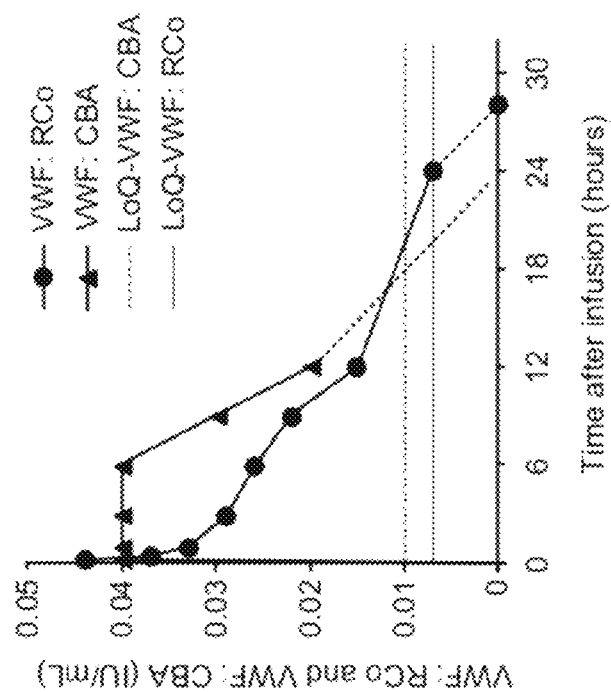


FIG. 13

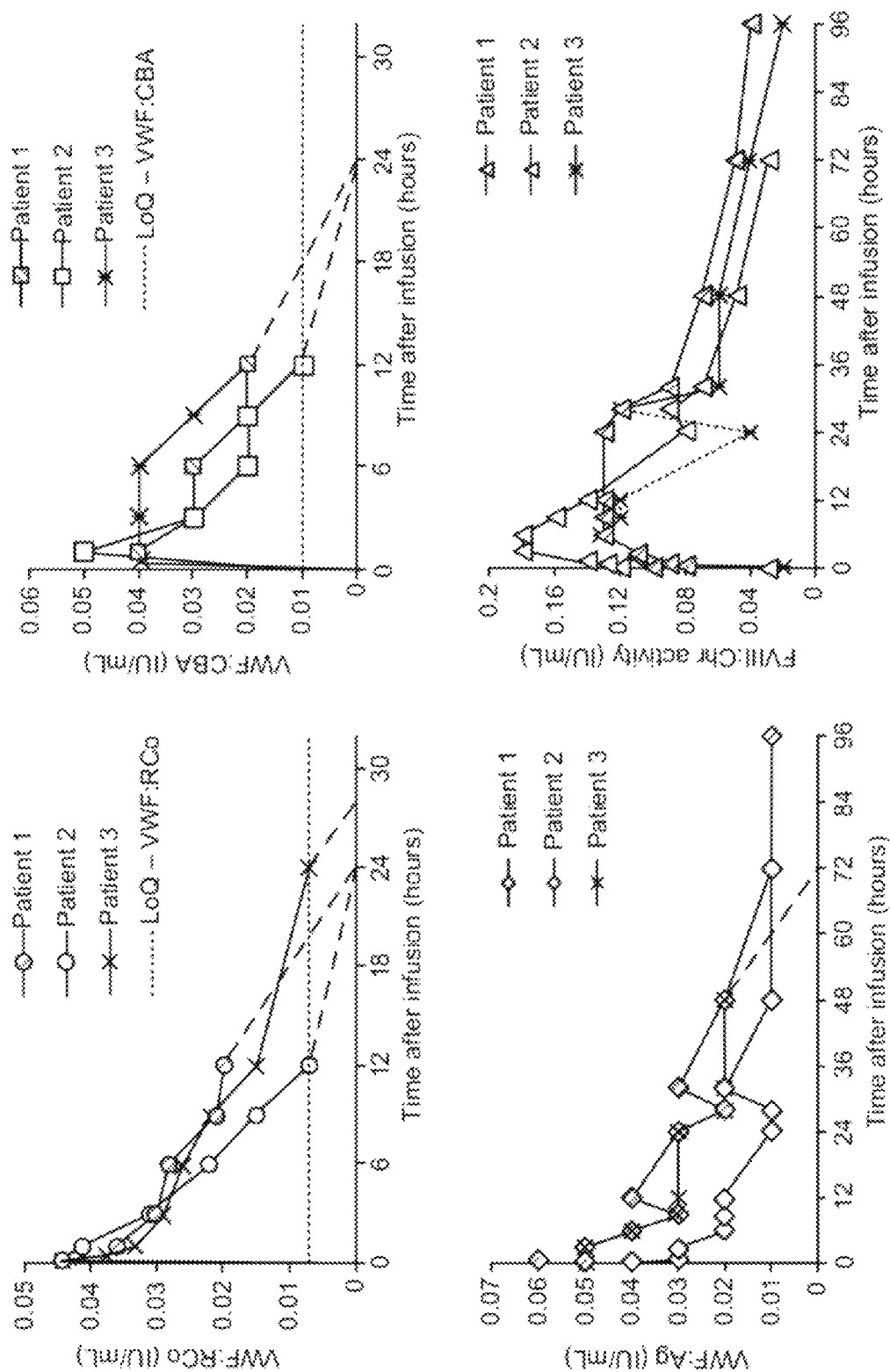


FIG. 15

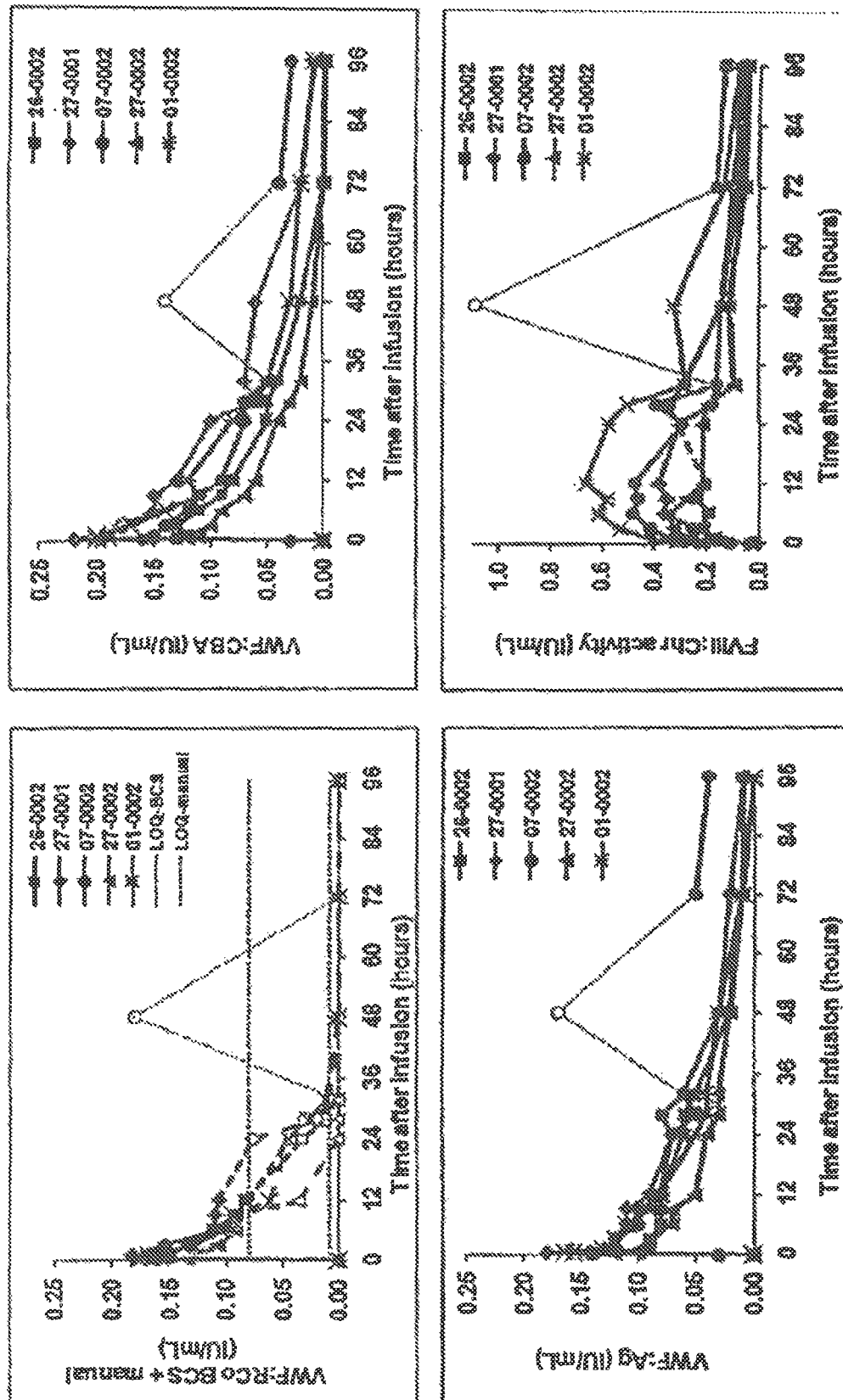


FIG. 16

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 2	rVFW/FVIII	AUC_{0-96h} [h^*U/dL]	5	1380.01	988.16; 3010.68	1860.05	942.5	50.67	1677.47
		AUC_{0-96h} [h^*U/dL]	5	1508.83	1056.99; 3072.84	1950.47	965.19	49.49	1766.01
		$AUMC_{0-96h}$ [h^*U/dL]	5	64516.47	33185.37; 126406.6	72917.08	41521.23	56.94	63274.8
		$T_{1/2}$ [hours]	5	22.86	17.81; 24.48	21.93	2.54	11.56	21.8
		MRT [hours]	5	35.91	27.51; 42.73	36.22	6.08	16.78	35.79
		Cl [$mL/kg/hours$]	5	0.53	0.24; 0.71	0.47	0.21	44.92	0.43
		V_{ss} [mL/kg]	5	17.12	9.26; 24	16.63	6.91	41.52	15.4
		C_{max} [U/dL]	5	34	32; 98	51.8	28.99	55.96	46.39
		T_{max} [hours]	5	12.22	6.03; 48.07	21.15	17.1	80.87	16.27
		IR [(U/dL)/(U VWF:RCO/ kg)]	5	4.53	3.98; 13.11	6.86	3.93	57.33	6.11
		$T_{1/2max}$ [hours]	1	32.57	NA	32.57	NA	NA	32.57
		T_{60ms} [hours]	1	3207.83	NA	3207.83	NA	NA	3207.83

FIG. 17

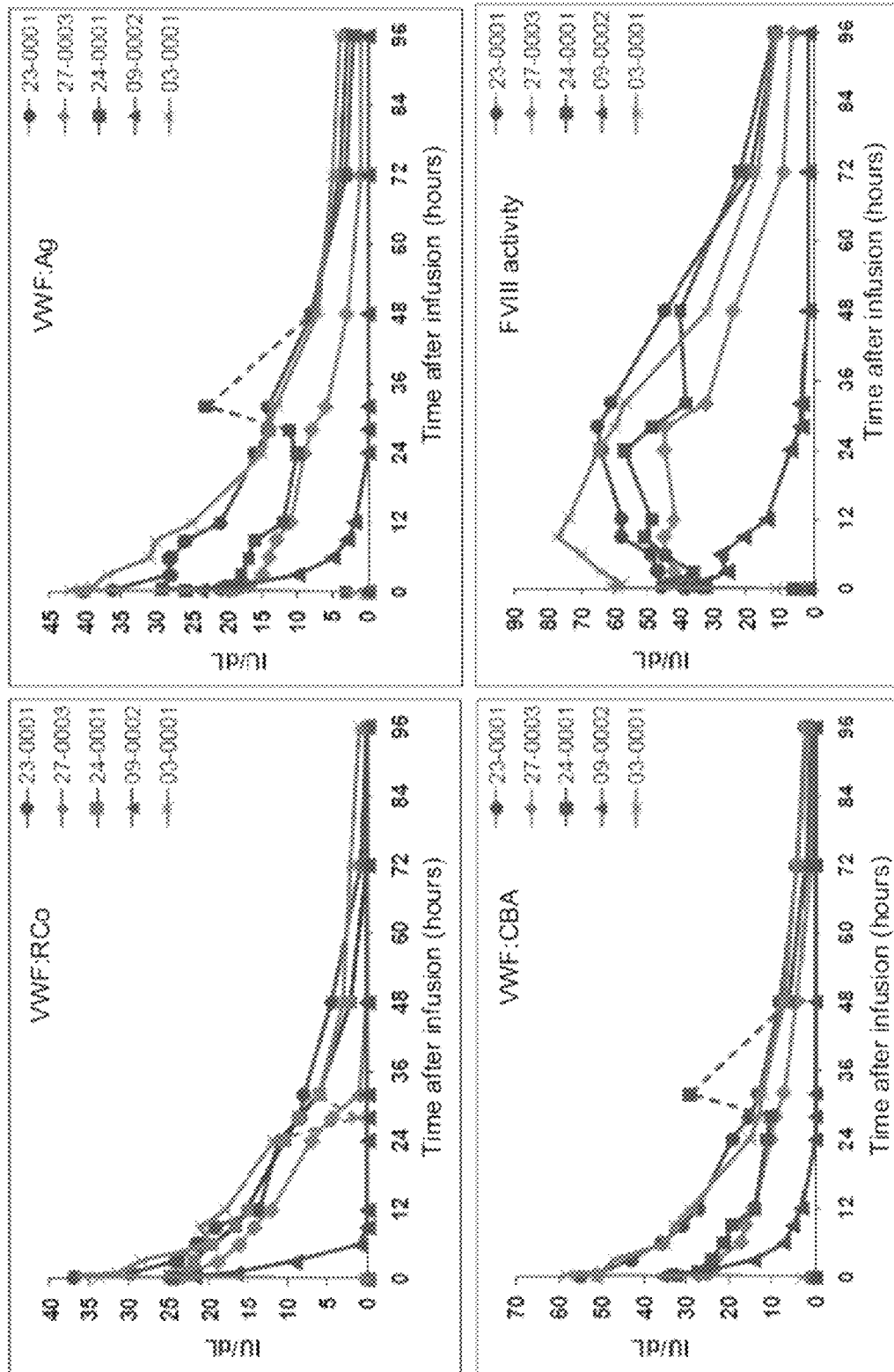


FIG. 18

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 3	rVFW/FVIII	AUC _{0-96h} [h*U/dL]	4	2745.17	2093.62; 3639.65	2805.91	635.05	22.63	2752.8
		AUC _{0-144h} [h*U/dL]	4	2858.66	2172.08; 3947.87	2959.32	740.27	25.01	2892.1
		AUMC _{0-144h} [h ² *U/dL]	4	100089.53	71254.38; 168025.02	109864.62	47247.29	43.01	102450.3 ₃
		T _{1/2} [hours]	4	20.72	14.43; 25.93	20.45	5.19	25.36	19.94
		MRT [hours]	4	37.53	25.97; 43.16	36.05	8.21	22.77	35.3
		Cl [mL/kg/hours]	4	0.7	0.51; 0.95	0.72	0.18	25.34	0.7
		V _{ss} [mL/kg]	4	25.32	18.9; 31.12	25.16	5.82	23.11	24.65
		C _{max} [U/dL]	4	57	42; 66	55.5	11.09	19.98	54.63
		T _{max} [hours]	4	16.45	6.1; 28.48	16.87	10.9	64.6	13.95
		IR [(U/dL)/(U VWF:RCO/kg)]	4	2.84	2.04; 3.31	2.75	0.58	20.9	2.71
		T _{adipex} [hours]	0	NA					
		T _{toxin} [hours]	0	NA					

FIG. 19

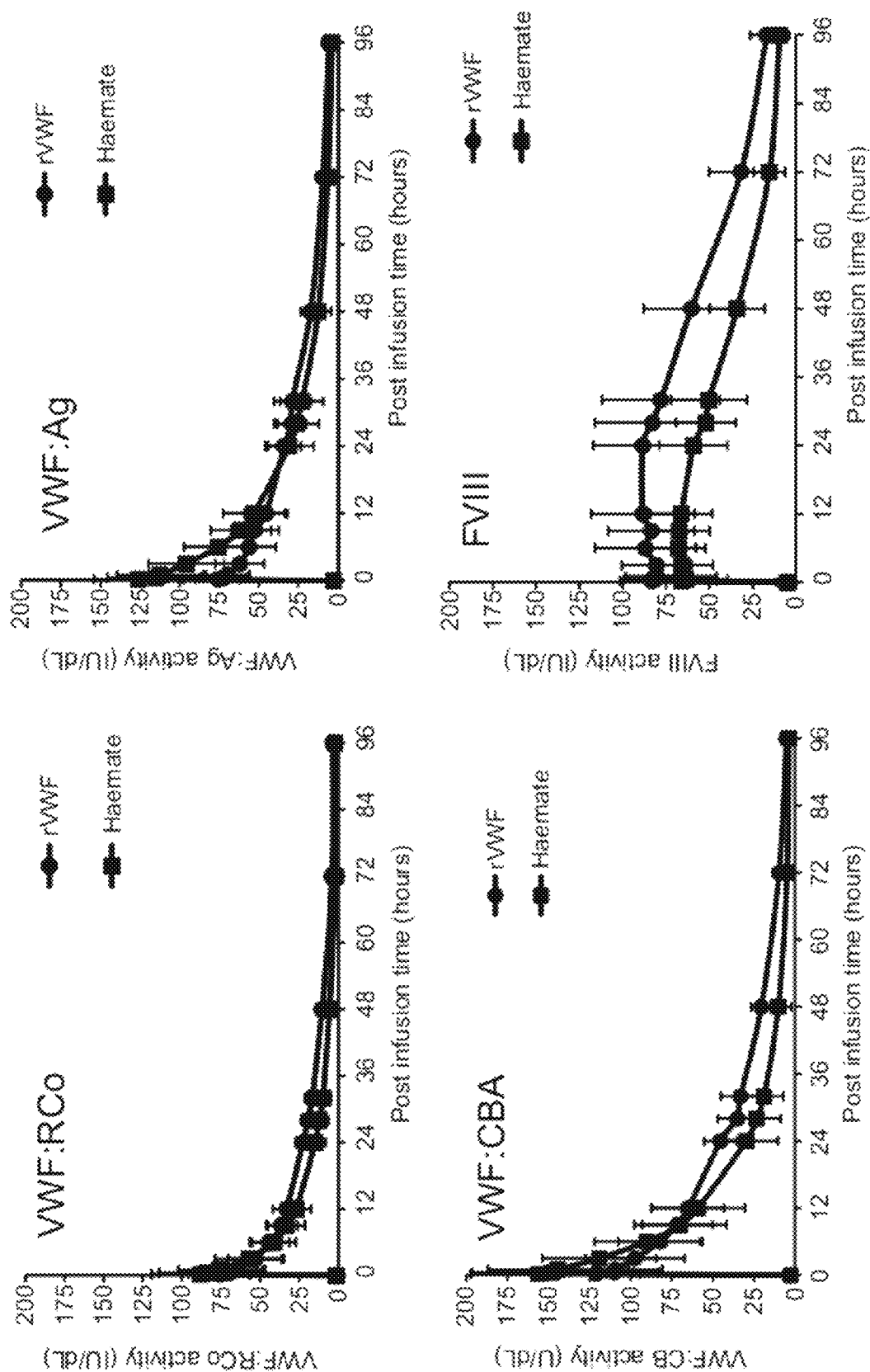


FIG. 20

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 4A	rVWF/FVIII	AUC _{0-96h} [h*U/dL]	19	4895.54	4049.13; 5239.58	4882.21	1993.76	40.84	4162.04
		AUC _{0-96h} [h*U/dL]	19	5287.34	4321.1; 5913.43	5375.56	2380.4	44.28	4520.61
		AUMC _{0-96h} [h ² *U/dL]	19	198560.36	157848.13; 259386.51	233248.57	157945.3	67.72	153532.1 ₄
		T _{1/2} [hours]	18	24.39	21.41; 25.78	24.3	6.47	26.64	23.48
		MRT [hours]	19	39.56	36.69; 43.32	38.92	12.43	31.93	34.06
		Cl [mL/kg/hours]	19	0.95	0.85; 1.16	1.57	2.67	169.59	1.04
		V _{ss} [mL/kg]	19	37.27	32.42; 38.84	37.12	11.63	31.34	35.28
		C _{max} [U/dL]	19	90	85; 99	94.53	22.68	24	92.07
		T _{max} [hours]	19	12.3	8.73; 24.22	15.94	11.01	69.07	9.14
		IR [(U/dL)/(U VWF:RCO/kg)]	19	1.83	1.74; 2.01	2.07	0.82	39.39	1.97
		T _{1/2α} [hours]	1	36.66	NA	36.66	NA	NA	36.66
		T _{1/2β} [hours]	1	182.27	NA	182.27	NA	NA	182.27
		AUC _{0-96h} [h*U/dL]	17	3061.61	2911.05; 4270.87	3185.02	1219.32	38.28	2943.65
pVWF/FVIII	pVWF/FVIII	AUC _{0-96h} [h*U/dL]	17	3209.44	3026.55; 4394.81	3361.13	1350.1	40.17	3092.1
		AUMC _{0-96h} [h ² *U/dL]	17	100993.49	83515.77; 149051.17	118375.88	72364.04	61.13	99238.4
		T _{1/2} [hours]	17	18.07	17.52; 21.59	19.1	5.13	26.84	18.46
		MRT [hours]	17	30.33	27.68; 38.41	32.7	7.47	22.83	31.94
		Cl [mL/kg/hours]	17	1.73	1.56; 2.37	1.89	0.75	39.96	1.75
		V _{ss} [mL/kg]	17	59.01	45.8; 67.85	58.24	17.15	29.44	55.94
		C _{max} [U/dL]	17	71	58; 80	70.59	15.87	22.48	68.92
		T _{max} [hours]	17	6.63	3.25; 12.08	9.83	9.6	97.74	5.96
		IR [(U/dL)/(U VWF:RCO/kg)]	17	1.17	1.14; 1.5	1.31	0.33	24.99	1.27
		T _{1/2α} [hours]	5	26.03	0.66; 42.02	20.5	18.95	92.42	7.05
		T _{1/2β} [hours]	5	81.94	24.3; 668.45	291.55	337.7	115.83	121.36

FIG. 21

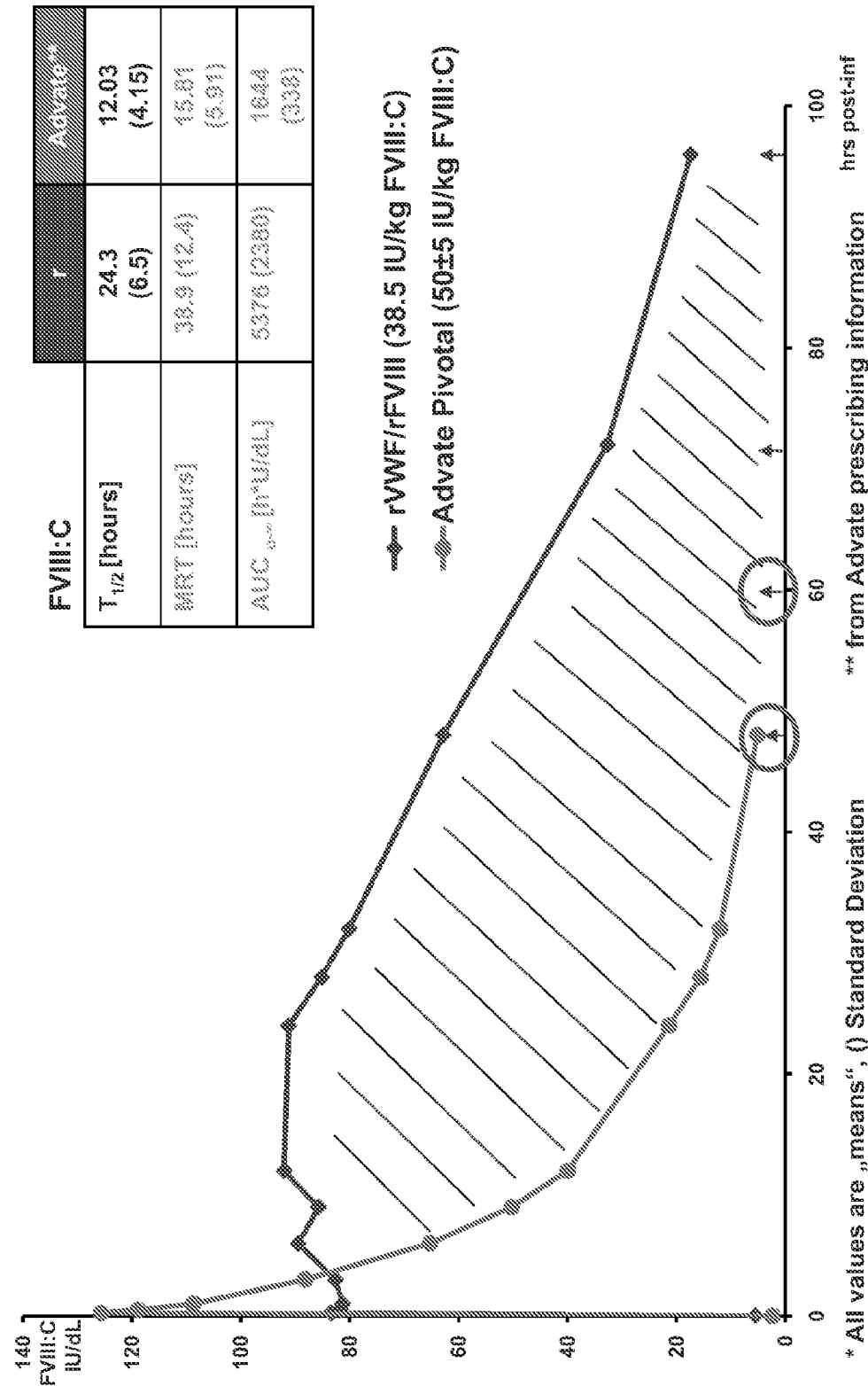
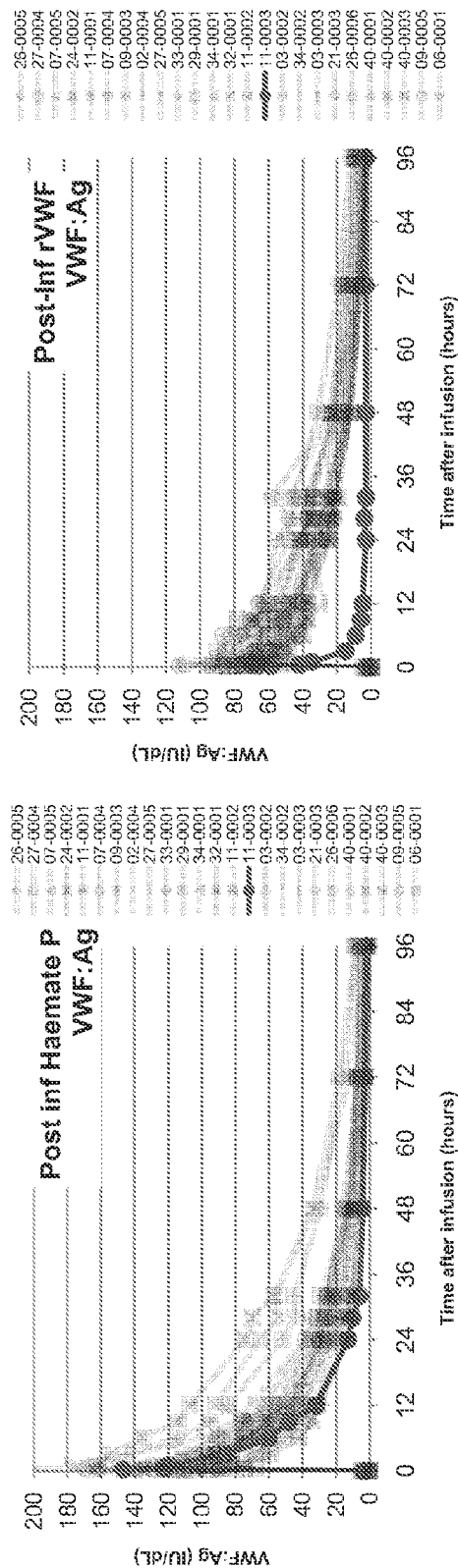


FIG. 22

Timepoint	Pre-Inf pdVWF/pdFVIII	Post-Inf pdVWF/pdFVIII	Post-Inf rVWF/rFVIII Study End
Binding Antibodies			
Binding anti-VWF Ab			
Titer binding anti-VWF Ab	Pos 1/1280	Pos 1/5120	Pos 1/5120
Confirmation anti-VWF Ab	Specific	Specific	Specific
Inhibiting Antibodies			
Ab to VWF: RCo (BU/mL)	<1	<1	<1
Ab to VWF:CB (BU/mL)	<1	<1	<1
Ab to VWF:FVIII-B (BU/mL)	<1	<1	<1
Ab to FVIII (BU/mL)	<0.4	<0.4	<0.4



1

TREATMENT OF COAGULATION DISEASE BY ADMINISTRATION OF RECOMBINANT VWF

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Patent Application No. 61/495,884, filed Jun. 10, 2011, U.S. Patent Application No. 61/511,901, filed Jul. 26, 2011, and U.S. Patent Application No. 61/523,790, filed Aug. 15, 2011, the disclosures of which are expressly incorporated herein by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

Coagulation diseases, such as von Willebrand Disease (VWD) and Hemophilia, generally result from a deficiency in the coagulation cascade. "von Willebrand Disease" refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump together and stick to the blood vessel wall, which is necessary for normal blood clotting. Hemophilia A refers to a deficiency of Factor VIII activity, whereas Hemophilia B refers to a Factor IX deficiency. Current treatment for these coagulopathies includes a replacement therapy using pharmaceutical preparations comprising the normal coagulation factor.

Replacement therapy in VWD and Hemophilia A patients involves the repeated administration of preparations containing normal coagulation factors via intravenous infusion, which can constitute a heavy load on the life of these patients, particularly when venous access is difficult to achieve. It would be advantageous if the frequency of infusions could be reduced. One potentially viable therapy is to stabilize Factor VIII through its association with a second molecule, such as von Willebrand Factor (VWF), with the result that plasma half-life of Factor VIII is increased.

VWF is a glycoprotein circulating in plasma as a series of multimers ranging in size from about 500 to 20,000 kD. The full length of cDNA of VWF has been cloned; the polypeptide corresponds to amino acid residues 23 to 764 of the full length prepro-VWF (Eikenboom et al (1995) Haemophilia 1, 77-90). Multimeric forms of VWF are composed of 250 kD polypeptide subunits linked together by disulfide bonds. VWF mediates the initial platelet adhesion to the sub-endothelium of the damaged vessel wall, with the larger multimers exhibiting enhanced hemostatic activity. Multimerized VWF binds to the platelet surface glycoprotein Gp1b α , through an interaction in the A1 domain of VWF, facilitating platelet adhesion. Other sites on VWF mediate binding to the blood vessel wall. Thus, VWF forms a bridge between the platelet and the vessel wall that is essential to platelet adhesion and primary hemostasis under conditions of high shear stress. Normally, endothelial cells secrete large polymeric forms of VWF and those forms of VWF that have a lower molecular weight arise from proteolytic cleavage. The multimers of exceptionally large molecular masses are stored in the Weibel-Pallade bodies of the endothelial cells and liberated upon stimulation by agonists such as thrombin and histamine.

That FVIII pharmacokinetics are a function of VWF levels is supported by several previous observations. Reduction of FVIII binding activity in von Willebrand Disease (VWD), due to either reduced VWF protein levels or lowered FVIII binding affinity, results in reduced steady-state levels of endogenous FVIII (summarized in Castaman et al., Disorders

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of Hemostasis 88(1):94-108 (2003), and improving survival of VWF has been proposed as a viable strategy for improving FVIII stability (Denis et al., Thromb Haemost. 2008 February; 99(2):271-8; Turecek et al., Blood, 2006, 108(11): Abstract 1002). Among severe Hemophilia A patients, a correlation between pre-infusion VWF levels and the half-life of infused FVIII has been demonstrated by Fijnvandraat and colleagues (Fijnvandraat, et al., Br J Haematol. 1995 October; 91(2):474-6). In that study, patients with 200-300% of average VWF levels were seen to have a FVIII half-life of 15-29 hours compared to a mean of 12.5 hours in patients with normal VWF levels. In another study, patients with blood group O were demonstrated to have significantly lower VWF levels and shorter FVIII half-lives (15.3 hours) compared with those with blood group A (19.7 hours) (Vlot, et al. Thromb Haemost. 2000 January; 83(1):65-9). Chemically modified VWF has been shown to prolong survival of rFVIII (Turecek et al., J. Thromb. Haemost. 2007 Jul. 9; 5(2) abstract available at: <http://www.blackwellpublishing.com/isth2007/abstract.asp?id=64898>). As such, co-administration of rVWF and rFVIII is a viable strategy for the treatment of coagulation diseases such as von Willebrand Disease and Hemophilia A.

BRIEF SUMMARY OF THE INVENTION

Accordingly, the present invention provides methods and combinations for treating coagulation disease by administering recombinant von Willebrand Factor (rVWF) alone or in combination with recombinant Factor VIII (rFVIII) to a subject in need thereof, with the result that the in-vivo half-life of Factor VIII is increased.

In one aspect, the present invention provides a method for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, and wherein the rVWF has a higher specific activity than plasma derived Von Willebrand Factor.

In further embodiments and in accordance with the above, methods of the invention include co-administering to the subject recombinant Von Willebrand Factor (rVWF) and recombinant Factor VIII (rFVIII).

In further embodiments and in accordance with any of the above, the rVWF and rFVIII are administered together in a single composition.

In further embodiments and in accordance with any of the above, the subject is administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose.

In further embodiments and in accordance with any of the above, the subject is administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose.

In further embodiments and in accordance with any of the above, the subject is administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose.

In further embodiments and in accordance with any of the above, the subject is administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

In further embodiments and in accordance with any of the above, the rVWF used in methods of the invention is matured in vitro by treatment with Furin.

In further embodiments and in accordance with any of the above, the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture).

In further embodiments and in accordance with any of the above, the rFVIII and rVWF are produced through expression in the same cell culture.

In further embodiments, and in accordance with any of the above, the subject is administered rVWF no more than once every other day.

In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than twice a week.

In further aspects and in accordance with any of the above, the high molecular weight VWF multimer composition maintains the at least 20% VWF decamers or higher order multimers for at least 3 hours post-administration.

In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended by about 5 hours.

In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 12 hours.

In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 24 hours.

In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 36 hours.

In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 48 hours.

In further embodiments and in accordance with any of the above, wherein the Factor VIII half-life is extended for at least 72 hours.

In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

In further embodiments and in accordance with any of the above, 23 the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

In further embodiments and in accordance with any of the above, the rVWF has a specific activity of about 20-150 mU/ μ g.

In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 30% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 40% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 50% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is about 20-150 mU/ μ g; and (b) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, (b) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is at least about 20-150 mU/ μ g; and (c) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration of the rVWF is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 36 hours post-administration is at least 80% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 48 hours post-administration is at least 50% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 6 hours post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 12 hours post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 18 hours post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 24 hours post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 36 hours post-administration.

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In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 48 hours post-administration.

In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 72 hours post-administration.

In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF).

In further embodiments and in accordance with any of the above, the method comprises co-administering to the subject recombinant Factor VIII (rFVIII) and recombinant Von Willebrand Factor (rVWF).

In further embodiments and in accordance with any of the above, the rFVIII and rVWF are administered together in a single composition.

In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

In further embodiments and in accordance with any of the above, the rVWF is matured in vitro by treatment with Furin.

In further embodiments and in accordance with any of the above, the rVWF is expressed in mammalian cell culture.

In further embodiments and in accordance with any of the above, the rFVIII is expressed in mammalian cell culture.

In further embodiments and in accordance with any of the above, the mammalian culture comprises CHO cells.

In further embodiments and in accordance with any of the above, the rFVIII and rVWF are co-expressed in the same culture.

In further embodiments and in accordance with any of the above, the rFVIII and rVWF are co-purified.

In further embodiments and in accordance with any of the above, the rFVIII and rVWF are purified separately.

In further embodiments and in accordance with any of the above, a rFVIII/rVWF complex is reconstituted prior to administration.

In further embodiments and in accordance with any of the above, rVWF is treated with Furin prior to reconstituting the rFVIII/rVWF complex.

In further embodiments and in accordance with any of the above, the reconstituted rFVIII/rVWF complex is treated with Furin.

In further embodiments and in accordance with any of the above, the Furin is recombinant Furin.

In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once daily.

In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once every other day.

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In further embodiments and in accordance with any of the above, the subject is co-administered rVWF no more than once every third day.

In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once every fourth day.

In further embodiments and in accordance with any of the above, the subject is administered between 1.5 IU/kg FVIII:C and 150 IU/kg FVIII:C per dose.

10 In further embodiments and in accordance with any of the above, the subject is administered between 10 IU/kg FVIII:C and 100 IU/kg FVIII:C per dose.

In further embodiments and in accordance with any of the above, the subject is administered between 25 IU/kg FVIII:C and 75 IU/kg FVIII:C per dose.

15 In further embodiments and in accordance with any of the above, the subject is administered between 40 IU/kg FVIII:C and 60 IU/kg FVIII:C per dose.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 36 hours post-administration is at least 80% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

30 In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 48 hours post-administration is at least 50% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 10% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 20% VWF decamers or higher order multimers.

35 In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 30% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 40% VWF decamers or higher order multimers.

40 In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 50% VWF decamers or higher order multimers.

In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable in vitro for at least 3 hours post-administration.

In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable in vitro for at least 6 hours post-administration.

65 In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable in vitro for at least 12 hours post-administration.

In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable in vitro for at least 18 hours post-administration.

In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable in vitro for at least 24 hours post-administration.

In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable in vitro for at least 36 hours post-administration.

In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable in vitro for at least 48 hours post-administration.

In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable in vitro for at least 72 hours post-administration.

In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 12 hours.

In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 24 hours.

In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 36 hours.

In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 48 hours.

In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 72 hours.

In further embodiments and in accordance with any of the above, wherein co-administered rFVIII activity is stabilized for at least 12 hours.

In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 24 hours.

In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 36 hours.

In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 48 hours.

In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 72 hours.

In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized by extending the half-life of the rFVIII in vivo.

In further embodiments and in accordance with any of the above, FVIII half-life is extended by about five hours as compared to a patient administered pdFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 36 hours in a patient administered said rFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 48 hours in a patient administered said rFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 72 hours in a patient administered said rFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 90 hours in a patient administered said rFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 120 hours in a patient administered said rFVIII.

In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 168 hours in a patient administered said rFVIII.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. A schematic of the study design assessing tolerability and safety after single doses of rVWF:rFVIII.

FIG. 2. Pharmacokinetic data. (A) provides PK data for rVWF/rFVIII and pdVWF/pdFVIII. (B) provides data on progressive loss of high molecular weight rVWF upon exposure to ADAMTS13.

FIG. 3. Pharmacokinetic data showing FVIII PK for rVWF/rFVIII and pdVWF/pdFVIII.

FIG. 4. Table summarizing patient demographics for the study.

FIG. 5. Pharmacokinetic data of rVWF/rFVIII and pdVWF/pdFVIII treatment of Cohort 4A.

FIG. 6. SDS-PAGE data on VWF multimer cleavage by ADAMTS13.

FIG. 7. Pharmacokinetic data of rVWF/rFVIII and pdVWF/pdFVIII treatment of Cohort 4A.

FIG. 8. Summary of adverse events from the study.

FIG. 9. rVWF PK parameters data from the study.

FIG. 10. rVWF PK data from Patient 1.

FIG. 11. rVWF PK data from Patient 2.

FIG. 12. rVWF PK data from Patient 3.

FIG. 13. Comparison of rVWF PK in Patients 1, 2 and 3—comparison of the VWF parameters and FVIII activity.

FIG. 14. FVIII activity across all cohorts in the study.

FIG. 15. rVWF PK in patients of Cohort 2—comparison of VWF parameters and FVIII activity.

FIG. 16. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 2.

FIG. 17. rVWF PK in all patients of Cohort 3—comparison of plasma parameters for VWF and FVIII.

FIG. 18. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 3.

FIG. 19. Data from patients in Cohort 4.

FIG. 20. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 4A.

FIG. 21. Pharmacokinetic data of FVIII:C comparing co-administered rVWF and rFVIII to Advate Pivotal.

FIG. 22. Antibody summary for a subject receiving co-administered pdVWF/pdFVIII or rVWF/rFVIII.

DETAILED DESCRIPTION OF THE INVENTION

Overview

The present invention provides compositions and methods for treating coagulation disease in a subject by administering recombinant von Willebrand Factor (rVWF) alone or in combination with Factor VIII (which can be recombinant or plasma derived). In some aspects, the compositions and methods of the present invention are used for treating coagulation diseases such as von Willebrand Disease (VWD) or Hemophilia A.

In one aspect, rVWF administered to the subject provides increased stability for in vivo Factor VIII (FVIII) activity as

compared to FVIII stability due to administered plasma derived VWF, allowing for lower doses and/or frequency of treatment than in traditional treatments for coagulation diseases. Increased stability of FVIII activity and levels of FVIII can be measured using methods known in the art and described herein, including standard assays such as one-stage clotting assays, chromogenic assays, and immunoassays (see for example Lippi et al., *Blood Coagulation & Fibrinolysis*, 2009, 20(1): 1-3 and Chandler et al., *Am J. Clin. Pathol.*, 2003, 120:34-39, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays of FVIII level and activity). As shown in FIG. 20, average FVIII half-life was increased by rVWF by 5.2 hours over the half-life for patients receiving pdVWF. FIGS. 2 and 7 also show increases in FVIII activity in patients administered rVWF as compared to those administered pdVWF: FIG. 2 shows that average FVIII half-life was increased by 4.7 hours for patients administered rVWF as compared to patients administered pdVWF, and the data from Cohort 4A in FIG. 7 shows an increase in FVIII half-life of 5.3 hours for patients administered rVWF as compared to patients administered pdVWF. In addition, as shown in FIG. 21, the half-life of plasma FVIII is increased by 12.27 hours in VWD patients receiving rVWF in combination with rFVIII as compared to patients receiving FVIII (i.e., Advate) alone.

In a further aspect, the administration of rVWF stabilizes endogenous and/or co-administered FVIII activity, with the result that the *in vivo* half-life and/or activity of FVIII is increased. In embodiments in which rVWF and FVIII are co-administered, the rVWF and FVIII can be administered to the subject together in a single composition. In further embodiments, neither rVWF nor FVIII are modified with a water soluble polymer. In other embodiments, either the rVWF or FVIII or both are modified with a water soluble polymer. As will be appreciated, in embodiments in which rVWF is co-administered with FVIII, the FVIII may be recombinant or plasma derived.

In further aspects and in accordance with any of the above, the rVWF administered to the subject is a high molecular weight multimer composition comprising decamers or higher order multimers of rVWF. As discussed above, the use of rVWF compositions of the invention provide therapeutic flexibility to dose (or re-dose) with or without FVIII (recombinant or plasma derived). In further embodiments, the rVWF administered to the subject is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers. In specific embodiments, the rVWF administered to subjects is not modified with a water soluble polymer.

In still further aspects, the rVWF administered to the subject has a higher specific activity than pdVWF.

In a still further aspect, the rVWF alone or in combination with pdFVIII or rFVIII is administered to the subject no more than twice a week.

In a yet further aspect, the rVWF is processed with Furin prior to administration to the subject. In certain embodiments, the rVWF is processed with recombinant Furin.

In further aspects, the rVWF of use in the present invention is produced in accordance with methods known in the art and described for example in US 2012/0035110, filed Jul. 8, 2011 and U.S. Pat. No. 8,173,597, issued May 8, 2012, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to rVWF compositions and methods for producing those compositions.

In accordance with any of the above, rVWF alone or in combination with FVIII is used to treat patients with coagu-

lation diseases, such as VWD and Hemophilia A. Patients with VWD have some level of FVIII, but the stability of that FVIII is generally compromised because these patients lack VWF. Treatment of VWD patients may in some embodiments involve an initial treatment with both rVWF and rFVIII followed by repeated administrations of rVWF alone. In other embodiments, the initial treatment may be with rVWF alone while subsequent repeated administrations are with both rVWF and rFVIII, or the initial and subsequent repeat administrations may all include a co-administration of both rVWF and rFVIII. Similarly, Hemophilia A patients (who lack FVIII) may receive an initial treatment of both rVWF and rFVIII, and subsequent repeat treatments may comprise the administration of rFVIII alone or rVWF alone. In other embodiments, the initial treatment may be rFVIII alone while the subsequent repeat treatments involve co-administration of rVWF and rFVIII.

DEFINITIONS

As used herein, "rVWF" refers to recombinant VWF.

As used herein, "rFVIII" refers to recombinant FVIII.

The term "recombinant" when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

As used herein, "recombinant VWF" includes VWF obtained via recombinant DNA technology. In certain embodiments, VWF proteins of the invention can comprise a construct, for example, prepared as in WO 1986/06096 published on Oct. 23, 1986 and U.S. patent application Ser. No. 07/559,509, filed on Jul. 23, 1990, in the name of Ginsburg et al., which is incorporated herein by reference with respect to the methods of producing recombinant VWF. The VWF in the present invention can include all potential forms, including the monomeric and multimeric forms. It should also be understood that the present invention encompasses different forms of VWF to be used in combination. For example, the VWF of the present invention may include different multimers, different derivatives and both biologically active derivatives and derivatives not biologically active.

In the context of the present invention, the recombinant VWF embraces any member of the VWF family from, for example, a mammal such as a primate, human, monkey, rabbit, pig, rodent, mouse, rat, hamster, gerbil, canine, feline, and biologically active derivatives thereof. Mutant and variant VWF proteins having activity are also embraced, as are functional fragments and fusion proteins of the VWF proteins. Furthermore, the VWF of the invention may further comprise tags that facilitate purification, detection, or both. The VWF described herein may further be modified with a therapeutic moiety or a moiety suitable imaging *in vitro* or *in vivo*.

As used herein, "plasma-derived VWF (pdVWF)" includes all forms of the protein found in blood including the mature VWF obtained from a mammal having the property of *in vivo*-stabilizing, e.g. binding, of at least one FVIII molecule.

The term "highly multimeric VWF" or "high molecular weight VWF" refers to VWF comprising at least 10 subunits, or 12, 14, or 16 subunits, to about 20, 22, 24 or 26 subunits or more. The term "subunit" refers to a monomer of VWF. As is known in the art, it is generally dimers of VWF that polymer-

ize to form the larger order multimers. (see Turecek et al., *Semin. Thromb. Hemost.* 2010, 36(5): 510-521 which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings regarding multimer analysis of VWF).

As used herein, the term “factor VIII” or “FVIII” refers to any form of factor VIII molecule with the typical characteristics of blood coagulation factor VIII, whether endogenous to a patient, derived from blood plasma, or produced through the use of recombinant DNA techniques, and including all modified forms of factor VIII. Factor VIII (FVIII) exists naturally and in therapeutic preparations as a heterogeneous distribution of polypeptides arising from a single gene product (see, e.g., Andersson et al., *Proc. Natl. Acad. Sci. USA*, 83:2979-2983 (1986)). Commercially available examples of therapeutic preparations containing Factor VIII include those sold under the trade names of HEMOFIL M, ADVATE, and RECOMBINATE (available from Baxter Healthcare Corporation, Deerfield, Ill., U.S.A.).

As used herein, “plasma FVIII activity” and “in vivo FVIII activity” are used interchangeably. The in vivo FVIII activity measured using standard assays may be endogenous FVIII activity, the activity of a therapeutically administered FVIII (recombinant or plasma derived), or both endogenous and administered FVIII activity. Similarly, “plasma FVIII” refers to endogenous FVIII or administered recombinant or plasma derived FVIII.

As used herein “von Willebrand Disease” refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump together and stick to the blood vessel wall, which is necessary for normal blood clotting. As described in further detail herein, there are several types of Von Willebrand disease.

As used herein, the terms “hemophilia” or “haemophilia” refer to a group of disease states broadly characterized by reduced blood clotting or coagulation. Hemophilia may refer to Type A, Type B, or Type C hemophilia, or to the composite of all three diseases types. Type A hemophilia (hemophilia A) is caused by a reduction or loss of factor VIII (FVIII) activity and is the most prominent of the hemophilia subtypes. Type B hemophilia (hemophilia B) results from the loss or reduction of factor IX (FIX) clotting function. Type C hemophilia (hemophilia C) is a consequence of the loss or reduction in factor XI (FXI) clotting activity. Hemophilia A and B are X-linked diseases, while hemophilia C is autosomal. Common treatments for hemophilia include both prophylactic and on-demand administration of clotting factors, such as FVIII, FIX, including Bebulin®-VH, and FXI, as well as FEIBA-VH, desmopressin, and plasma infusions.

The terms “isolated,” “purified,” or “biologically pure” refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. VWF is the predominant species present in a preparation is substantially purified. The term “purified” in some embodiments denotes that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. In other embodiments, it means that the nucleic acid or protein is at least 50% pure, more preferably at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more pure. “Purify” or “purification” in other embodiments means removing at least one contaminant from the composition to be purified. In this sense, purification does not require that the purified compound be homogenous, e.g., 100% pure.

As used herein, “administering” (and all grammatical equivalents) includes intravenous administration, intramuscular administration, subcutaneous administration, oral administration, administration as a suppository, topical contact, intraperitoneal, intralesional, or intranasal administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route including parenteral, and transmucosal (e.g., oral, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc.

The terms “therapeutically effective amount or dose” or “therapeutically sufficient amount or dose” or “effective or sufficient amount or dose” refer to a dose that produces therapeutic effects for which it is administered. For example, a therapeutically effective amount of a drug useful for treating hemophilia can be the amount that is capable of preventing or relieving one or more symptoms associated with hemophilia. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

As used herein, the terms “patient” and “subject” are used interchangeably and refer to a mammal (preferably human) that has a disease or has the potential of contracting a disease.

As used herein, the term “about” denotes an approximate range of plus or minus 10% from a specified value. For instance, the language “about 20%” encompasses a range of 18-22%.

As used herein, the term “half-life” refers to the period of time it takes for the amount of a substance undergoing decay (or clearance from a sample or from a patient) to decrease by half.

Compositions of the Invention

The present invention utilizes compositions comprising recombinant von Willebrand Factor (rVWF) for treatment of coagulation disease, such as VWD and Hemophilia A. In some embodiments, the present invention utilizes rVWF in combination with Factor VIII (FVIII). The co-administered FVIII may be recombinant (rFVIII) or plasma derived (pd-FVIII). In preferred aspects, the compositions of the present invention stabilize in vivo Factor VIII activity (also referred to herein as plasma Factor VIII activity) such that the in vivo half-life of Factor VIII is extended as compared to that in subjects that have not been administered rVWF or that have been administered pdVWF. Measuring the extent to which rVWF stabilizes FVIII activity (including extension of FVIII half-life) can be carried out using methods known in the art. The level of FVIII activity can be measured by, for instance, one-stage clotting assays, chromogenic assays, and immunoassays (see for example Lippi et al., *Blood Coagulation & Fibrinolysis*, 2009, 20(1): 1-3, European Pharmacopoeia (Ph. Eur., 3rd ed. 1997: 2.7.4), and Chandler et al., *Am J. Clin. Pathol.*, 2003, 120:34-39, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays of FVIII level and activity).

In certain embodiments, VWF proteins of the invention may comprise a construct, for example, prepared as in WO 1986/06096 published on Oct. 23, 1986 and U.S. patent appli-

cation Ser. No. 07/559,509, filed on Jul. 23, 1990, in the name of Ginsburg et al., which is incorporated herein by reference with respect to the methods of producing recombinant VWF. The VWF useful for the present invention includes all potential forms, including the monomeric and multimeric forms. One particularly useful form of VWF are homo-multimers of at least two VWFs. The VWF proteins may be either a biologically active derivative, or when to be used solely as a stabilizer for FVIII the VWF may be of a form not biologically active. It should also be understood that the present invention encompasses different forms of VWF to be used in combination. For example, a composition useful for the present invention may include different multimers, different derivatives and both biologically active derivatives and derivatives not biologically active.

In primary hemostasis VWF serves as a bridge between platelets and specific components of the extracellular matrix, such as collagen. The biological activity of VWF in this process can be measured by different in vitro assays (Turecek et al., *Semin. Thromb. Hemost.* 28: 149-160, 2002). The ristocetin cofactor assay is based on the agglutination of fresh or formalin-fixed platelets induced by the antibiotic ristocetin in the presence of VWF. The degree of platelet agglutination depends on the VWF concentration and can be measured by the turbidimetric method, e.g. by use of an aggregometer (Weiss et al., *J. Clin. Invest.* 52: 2708-2716, 1973; Macfarlane et al., *Thromb. Diath. Haemorrh.* 34: 306-308, 1975). The second method is the collagen binding assay, which is based on ELISA technology (Brown et Bosak, *Thromb. Res.* 43: 303-311, 1986; Favalaro, *Thromb. Haemost.* 83: 127-135, 2000). A microtiter plate is coated with type I or III collagen. Then the VWF is bound to the collagen surface and subsequently detected with an enzyme-labeled polyclonal antibody. The last step is the substrate reaction, which can be photometrically monitored with an ELISA reader. As provided herein, the specific Ristocetin Cofactor activity of the VWF (VWF:RCO) of the present invention is generally described in terms of mU/ μ g of VWF, as measured using in vitro assays.

An advantage of the rVWF compositions of the present invention over pdVWF is that rVWF exhibits a higher specific activity than pdVWF. In some embodiments, the rVWF of the invention has a specific activity of at least about 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150 or more mU/ μ g. In one embodiment, rVWF used in the methods described herein has a specific activity of from 20 mU/ μ g to 150 mU/ μ g. In another embodiment, the VWF has a specific activity of from 30 mU/ μ g to 120 mU/ μ g. In another embodiment, the rVWF has a specific activity from 40 mU/ μ g to 90 mU/ μ g. In yet another embodiment, the rVWF has a specific activity selected from variations 1 to 133 found in Table 1.

TABLE 1

Exemplary embodiments for the specific activity of rVWF found in the compositions and used in the methods provided herein.	
(mU/ μ g)	
20	Var. 1
22.5	Var. 2
25	Var. 3
27.5	Var. 4
30	Var. 5
32.5	Var. 6

TABLE 1-continued

Exemplary embodiments for the specific activity of rVWF found in the compositions and used in the methods provided herein.	
(mU/ μ g)	
35	Var. 7
37.5	Var. 8
40	Var. 9
42.5	Var. 10
45	Var. 11
47.5	Var. 12
50	Var. 13
52.5	Var. 14
55	Var. 15
57.5	Var. 16
60	Var. 17
62.5	Var. 18
65	Var. 19
67.5	Var. 20
70	Var. 21
72.5	Var. 22
75	Var. 23
77.5	Var. 24
80	Var. 25
82.5	Var. 26
85	Var. 27
87.5	Var. 28
90	Var. 29
92.5	Var. 30
95	Var. 31
97.5	Var. 32
100	Var. 33
105	Var. 34
110	Var. 35
115	Var. 36
120	Var. 37
125	Var. 38
130	Var. 39
135	Var. 40
140	Var. 41
145	Var. 42
150	Var. 43
20-150	Var. 44
20-140	Var. 45
20-130	Var. 46
20-120	Var. 47
20-110	Var. 48
20-100	Var. 49
20-90	Var. 50
20-80	Var. 51
20-70	Var. 52
20-60	Var. 53
20-50	Var. 54
20-40	Var. 55
30-150	Var. 56
30-140	Var. 57
30-130	Var. 58
30-120	Var. 59
30-110	Var. 60
30-100	Var. 61
30-90	Var. 62
30-80	Var. 63
30-70	Var. 64
30-60	Var. 65
30-50	Var. 66
30-40	Var. 67
40-150	Var. 68
40-140	Var. 69
40-130	Var. 70
40-120	Var. 71
40-110	Var. 72
40-100	Var. 73
40-90	Var. 74
40-80	Var. 75
40-70	Var. 76
40-60	Var. 77
40-50	Var. 78
50-150	Var. 79
50-140	Var. 80
50-130	Var. 81

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TABLE 1-continued

Exemplary embodiments for the specific activity of rVWF found in the compositions and used in the methods provided herein.	
(mU/ μ g)	
50-120	Var. 82
50-110	Var. 83
50-100	Var. 84
50-90	Var. 85
50-80	Var. 86
50-70	Var. 87
50-60	Var. 88
60-150	Var. 89
60-140	Var. 90
60-130	Var. 91
60-120	Var. 92
60-110	Var. 93
60-100	Var. 94
60-90	Var. 95
60-80	Var. 96
60-70	Var. 97
70-150	Var. 98
70-140	Var. 99
70-130	Var. 100
70-120	Var. 101
70-110	Var. 102
70-100	Var. 103
70-90	Var. 104
70-80	Var. 105
80-150	Var. 106
80-140	Var. 107
80-130	Var. 108
80-120	Var. 109
80-110	Var. 110
80-100	Var. 111
80-90	Var. 112
90-150	Var. 113
90-140	Var. 114
90-130	Var. 115
90-120	Var. 116
90-110	Var. 117
90-100	Var. 118
100-150	Var. 119
100-140	Var. 120
100-130	Var. 121
100-120	Var. 122
100-110	Var. 123
110-150	Var. 124
110-140	Var. 125
110-130	Var. 126
110-120	Var. 127
120-150	Var. 128
120-140	Var. 129
120-130	Var. 130
130-150	Var. 131
130-140	Var. 132
140-150	Var. 133

Var. = Variation

The rVWF of the present invention is highly multimeric comprising about 10 to about 40 subunits. In further embodiments, the multimeric rVWF produced using methods of the present invention comprise about 10-30, 12-28, 14-26, 16-24, 18-22, 20-21 subunits. In further embodiments, the rVWF is present in multimers varying in size from dimers to multimers of over 40 subunits (>10 million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. As shown in the multimer analysis in FIG. 2 (bottom panel), application of ADAMTS13 will cleave the ultra-large rVWF multimers over time, but during production (generally through expression in cell culture), rVWF compositions of the present invention are generally not exposed to ADAMTS13 and retain their highly multimeric structure.

In one embodiment, a rVWF composition used in the methods described herein has a distribution of rVWF oligomers

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characterized in that 95% of the oligomers have between 6 subunits and 20 subunits. In other embodiments, the a rVWF composition has a distribution of rVWF oligomers characterized in that 95% of the oligomers have a range of subunits selected from variations 458 to 641 found in Table 2.

TABLE 2

Exemplary embodiments for the distribution of rVWF oligomers found in the compositions and used in the methods provided herein.		
Subunits		
10	2-40	Var. 458
	2-38	Var. 459
	2-36	Var. 460
	2-34	Var. 461
	2-32	Var. 462
15	2-30	Var. 463
	2-28	Var. 464
	2-26	Var. 465
	2-24	Var. 466
	2-22	Var. 467
20	2-20	Var. 468
	2-18	Var. 469
	2-16	Var. 470
	2-14	Var. 471
	2-12	Var. 472
25	2-10	Var. 473
	2-8	Var. 474
	4-40	Var. 475
	4-38	Var. 476
	4-36	Var. 477
30	4-34	Var. 478
	4-32	Var. 479
	4-30	Var. 480
	4-28	Var. 481
	4-26	Var. 482
35	4-24	Var. 483
	4-22	Var. 484
	4-20	Var. 485
	4-18	Var. 486
	4-16	Var. 487
40	4-14	Var. 488
	4-12	Var. 489
	4-10	Var. 490
	4-8	Var. 491
	6-40	Var. 492
45	6-38	Var. 493
	6-36	Var. 494
	6-34	Var. 495
	6-32	Var. 496
	6-30	Var. 497
50	6-28	Var. 498
	6-26	Var. 499
	6-24	Var. 500
	6-22	Var. 501
	6-20	Var. 502
55	6-18	Var. 503
	6-16	Var. 504
	6-14	Var. 505
	6-12	Var. 506
	6-10	Var. 507
60	6-8	Var. 508
	8-40	Var. 509
	8-38	Var. 510
	8-36	Var. 511
	8-34	Var. 512
65	8-32	Var. 513
	8-30	Var. 514
	8-28	Var. 515
	8-26	Var. 516
	8-24	Var. 517
	8-22	Var. 518
	8-20	Var. 519
	8-18	Var. 520
	8-16	Var. 521
	8-14	Var. 522
	8-12	Var. 523
	8-10	Var. 524

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TABLE 2-continued

Exemplary embodiments for the distribution of rVWF oligomers found in the compositions and used in the methods provided herein.		
Subunits		
10-40	Var. 525	5
10-38	Var. 526	
10-36	Var. 527	
10-34	Var. 528	
10-32	Var. 529	
10-30	Var. 530	10
10-28	Var. 531	
10-26	Var. 532	
10-24	Var. 533	
10-22	Var. 534	
10-20	Var. 535	15
10-18	Var. 536	
10-16	Var. 537	
10-14	Var. 538	
10-12	Var. 539	
12-40	Var. 540	20
12-38	Var. 541	
12-36	Var. 542	
12-34	Var. 543	
12-32	Var. 544	
12-30	Var. 545	25
12-28	Var. 546	
12-26	Var. 547	
12-24	Var. 548	
12-22	Var. 549	
12-20	Var. 550	30
12-18	Var. 551	
12-16	Var. 552	
12-14	Var. 553	
14-40	Var. 554	
14-38	Var. 555	35
14-36	Var. 556	
14-34	Var. 557	
14-32	Var. 558	
14-30	Var. 559	
14-28	Var. 560	40
14-26	Var. 561	
14-24	Var. 562	
14-22	Var. 563	
14-20	Var. 564	
14-18	Var. 565	45
14-16	Var. 566	
16-40	Var. 567	
16-38	Var. 568	
16-36	Var. 569	
16-34	Var. 570	50
16-32	Var. 571	
16-30	Var. 572	
16-28	Var. 573	
16-26	Var. 574	
16-24	Var. 575	55
16-22	Var. 576	
16-20	Var. 577	
16-18	Var. 578	
18-40	Var. 579	
18-38	Var. 580	60
18-36	Var. 581	
18-34	Var. 582	
18-32	Var. 583	
18-30	Var. 584	
18-28	Var. 585	65
18-26	Var. 586	
18-24	Var. 587	
18-22	Var. 588	
18-20	Var. 589	
20-40	Var. 590	
20-38	Var. 591	
20-36	Var. 592	
20-34	Var. 593	
20-32	Var. 594	
20-30	Var. 595	
20-28	Var. 596	
20-26	Var. 597	
20-24	Var. 598	
20-22	Var. 599	

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TABLE 2-continued

Exemplary embodiments for the distribution of rVWF oligomers found in the compositions and used in the methods provided herein.		
Subunits		
22-40	Var. 600	5
22-38	Var. 601	
22-36	Var. 602	
22-34	Var. 603	
22-32	Var. 604	
22-30	Var. 605	10
22-28	Var. 606	
22-26	Var. 607	
22-24	Var. 608	
24-40	Var. 609	
24-38	Var. 610	15
24-36	Var. 611	
24-34	Var. 612	
24-32	Var. 613	
24-30	Var. 614	
24-28	Var. 615	20
24-26	Var. 616	
26-40	Var. 617	
26-38	Var. 618	
26-36	Var. 619	
26-34	Var. 620	25
26-32	Var. 621	
26-30	Var. 622	
26-28	Var. 623	
28-40	Var. 624	
28-38	Var. 625	30
28-36	Var. 626	
28-34	Var. 627	
28-32	Var. 628	
28-30	Var. 629	
30-40	Var. 630	35
30-38	Var. 631	
30-36	Var. 632	
30-34	Var. 633	
30-32	Var. 634	
32-40	Var. 635	40
32-38	Var. 636	
32-36	Var. 637	
32-34	Var. 638	
34-40	Var. 639	
36-38	Var. 640	45
38-40	Var. 641	

Var. = Variation

50

55

60

65

In one embodiment, a rVWF composition can be characterized according to the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer. For example, in one embodiment, at least 20% of rVWF molecules in a rVWF composition used in the methods described herein are present in an oligomeric complex of at least 10 subunits. In another embodiment, at least 20% of rVWF molecules in a rVWF composition used in the methods described herein are present in an oligomeric complex of at least 12 subunits. In yet other embodiments, a rVWF composition used in the methods provided herein has a minimal percentage (e.g., has at least X %) of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer (e.g., a multimer of at least Y subunits) according to any one of variations 134 to 457 found in Table 3 to Table 5.

TABLE 3

Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.							
Minimal Number of Subunits in rVWF Multimer							
	6	8	10	12	14	16	
Minimal Percentage of rVWF Molecules	10%	Var. 134	Var. 152	Var. 170	Var. 188	Var. 206	Var. 224
	15%	Var. 135	Var. 153	Var. 171	Var. 189	Var. 207	Var. 225
	20%	Var. 136	Var. 154	Var. 172	Var. 190	Var. 208	Var. 226
	25%	Var. 137	Var. 155	Var. 173	Var. 191	Var. 209	Var. 227
	30%	Var. 138	Var. 156	Var. 174	Var. 192	Var. 210	Var. 228
	35%	Var. 139	Var. 157	Var. 175	Var. 193	Var. 211	Var. 229
	40%	Var. 140	Var. 158	Var. 176	Var. 194	Var. 212	Var. 230
	45%	Var. 141	Var. 159	Var. 177	Var. 195	Var. 213	Var. 231
	50%	Var. 142	Var. 160	Var. 178	Var. 196	Var. 214	Var. 232
	55%	Var. 143	Var. 161	Var. 179	Var. 197	Var. 215	Var. 233
	60%	Var. 144	Var. 162	Var. 180	Var. 198	Var. 216	Var. 234
	65%	Var. 145	Var. 163	Var. 181	Var. 199	Var. 217	Var. 235
	70%	Var. 146	Var. 164	Var. 182	Var. 200	Var. 218	Var. 236
	75%	Var. 147	Var. 165	Var. 183	Var. 201	Var. 219	Var. 237
	80%	Var. 148	Var. 166	Var. 184	Var. 202	Var. 220	Var. 238
	85%	Var. 149	Var. 167	Var. 185	Var. 203	Var. 221	Var. 239
	90%	Var. 150	Var. 168	Var. 186	Var. 204	Var. 222	Var. 240
	95%	Var. 151	Var. 169	Var. 187	Var. 205	Var. 223	Var. 241

Var. = Variation

TABLE 4

Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.							
Minimal Number of Subunits in rVWF Multimer							
	18	20	22	24	26	28	
Minimal Percentage of rVWF Molecules	10%	Var. 242	Var. 260	Var. 278	Var. 296	Var. 314	Var. 332
	15%	Var. 243	Var. 261	Var. 279	Var. 297	Var. 315	Var. 333
	20%	Var. 244	Var. 262	Var. 280	Var. 298	Var. 316	Var. 333
	25%	Var. 245	Var. 263	Var. 281	Var. 299	Var. 317	Var. 335
	30%	Var. 246	Var. 264	Var. 282	Var. 300	Var. 318	Var. 336
	35%	Var. 247	Var. 265	Var. 283	Var. 301	Var. 319	Var. 337
	40%	Var. 248	Var. 266	Var. 284	Var. 302	Var. 320	Var. 338
	45%	Var. 249	Var. 267	Var. 285	Var. 303	Var. 321	Var. 339
	50%	Var. 250	Var. 268	Var. 286	Var. 304	Var. 322	Var. 340
	55%	Var. 251	Var. 269	Var. 287	Var. 305	Var. 323	Var. 341
	60%	Var. 252	Var. 270	Var. 288	Var. 306	Var. 324	Var. 342
	65%	Var. 253	Var. 271	Var. 289	Var. 307	Var. 325	Var. 343
	70%	Var. 254	Var. 272	Var. 290	Var. 308	Var. 326	Var. 344
	75%	Var. 255	Var. 273	Var. 291	Var. 309	Var. 327	Var. 345
	80%	Var. 256	Var. 274	Var. 292	Var. 310	Var. 328	Var. 346
	85%	Var. 257	Var. 275	Var. 293	Var. 311	Var. 329	Var. 347
	90%	Var. 258	Var. 276	Var. 294	Var. 312	Var. 330	Var. 348
	95%	Var. 259	Var. 277	Var. 295	Var. 313	Var. 331	Var. 349

Var. = Variation

TABLE 5

Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.							
Minimal Number of Subunits in rVWF Multimer							
	30	32	34	36	38	40	
Minimal Percentage of rVWF Molecules	10%	Var. 350	Var. 368	Var. 386	Var. 404	Var. 422	Var. 440
	15%	Var. 351	Var. 369	Var. 387	Var. 405	Var. 423	Var. 441
	20%	Var. 352	Var. 370	Var. 388	Var. 406	Var. 424	Var. 442
	25%	Var. 353	Var. 371	Var. 389	Var. 407	Var. 425	Var. 443
	30%	Var. 354	Var. 372	Var. 390	Var. 408	Var. 426	Var. 444
	35%	Var. 355	Var. 373	Var. 391	Var. 409	Var. 427	Var. 445
	40%	Var. 356	Var. 374	Var. 392	Var. 410	Var. 428	Var. 446

TABLE 5-continued

Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.						
Minimal Number of Subunits in rVWF Multimer						
	30	32	34	36	38	40
45% Var. 357	Var. 375	Var. 393	Var. 411	Var. 429	Var. 447	
50% Var. 358	Var. 376	Var. 394	Var. 412	Var. 430	Var. 448	
55% Var. 359	Var. 377	Var. 395	Var. 413	Var. 431	Var. 449	
60% Var. 360	Var. 378	Var. 396	Var. 414	Var. 432	Var. 450	
65% Var. 361	Var. 379	Var. 397	Var. 415	Var. 433	Var. 451	
70% Var. 362	Var. 380	Var. 398	Var. 416	Var. 434	Var. 452	
75% Var. 363	Var. 381	Var. 399	Var. 417	Var. 435	Var. 453	
80% Var. 364	Var. 382	Var. 400	Var. 418	Var. 436	Var. 454	
85% Var. 365	Var. 383	Var. 401	Var. 419	Var. 437	Var. 455	
90% Var. 366	Var. 384	Var. 402	Var. 420	Var. 438	Var. 456	
95% Var. 367	Var. 385	Var. 403	Var. 421	Var. 439	Var. 457	

Var. = Variation

In accordance with the above, the rVWF composition administered to the subject (with or without FVIII) generally comprises a significant percentage of high molecular weight (HMW) rVWF multimers. In further embodiments, the HMW rVWF multimer composition comprises at least 10%-80% rVWF decamers or higher order multimers. In further embodiments, the composition comprises about 10-95%, 20-90%, 30-85%, 40-80%, 50-75%, 60-70% decamers or higher order multimers. In further embodiments, the HMW rVWF multimer composition comprises at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% decamers or higher order multimers.

Assessment of the number and percentage of rVWF multimers can be conducted using methods known in the art, including without limitation methods using electrophoresis and size exclusion chromatography methods to separate VWF multimers by size, for example as discussed by Cumming et al, (J Clin Pathol. 1993 May; 46(5): 470-473, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assessment of VWF multimers). Such techniques may further include immunoblotting techniques (such as Western Blot), in which the gel is immunoblotted with a radiolabelled antibody against VWF followed by chemiluminescent detection (see for example Wen et al., (1993), J. Clin. Lab. Anal., 7: 317-323, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assessment of VWF multimers). Further assays for VWF include VWF:Antigen (VWF:Ag), VWF:Ristocetin Cofactor (VWF:RCof), and VWF:Collagen Binding Activity assay (VWF:CBA), which are often used for diagnosis and classification of Von Willebrand Disease. (see for example Favaloro et al., Pathology, 1997, 29(4): 341-456, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays for VWF).

In further embodiments, higher order rVWF multimers of the invention are stable for about 1 to about 90 hours post-administration. In still further embodiments, the higher order rVWF multimers are stable for about 5-80, 10-70, 15-60, 20-50, 25-40, 30-35 hours post-administration. In yet further embodiments, the higher order rVWF multimers are stable for at least 3, 6, 12, 18, 24, 36, 48, 72 hours post-administration. In certain embodiments the stability of the rVWF multimers is assessed in vitro.

In one embodiment, higher order rVWF multimers used in the compositions and methods provided herein have a half life of at least 12 hour post administration. In another embodiment, the higher order rVWF multimers have a half life of at least 24 hour post administration. In yet other embodiments, the higher order rVWF multimers have a half life selected from variations 642 to 1045 found in Table 6.

TABLE 6

Exemplary embodiments for the half-life of higher order rVWF multimers found in the compositions and used in the methods provided herein.		
Hours		
at least 1	Var. 642	
at least 2	Var. 643	
at least 3	Var. 644	
at least 4	Var. 645	
at least 5	Var. 646	
at least 6	Var. 647	
at least 7	Var. 648	
at least 8	Var. 649	
at least 9	Var. 650	
at least 10	Var. 651	
at least 11	Var. 652	
at least 12	Var. 653	
at least 14	Var. 654	
at least 16	Var. 655	
at least 18	Var. 656	
at least 20	Var. 657	
at least 22	Var. 658	
at least 24	Var. 659	
at least 27	Var. 660	
at least 30	Var. 661	
at least 33	Var. 662	
at least 36	Var. 663	
at least 39	Var. 664	
at least 42	Var. 665	
at least 45	Var. 666	
at least 48	Var. 667	
at least 54	Var. 668	
at least 60	Var. 669	
at least 66	Var. 670	
at least 72	Var. 671	
at least 78	Var. 672	
at least 84	Var. 673	
at least 90	Var. 674	
2-90	Var. 675	
2-84	Var. 676	
2-78	Var. 677	
2-72	Var. 678	
2-66	Var. 679	
2-60	Var. 680	
2-54	Var. 681	

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TABLE 6-continued

Exemplary embodiments for the half-life of higher order rVWF multimers
found in the compositions and used in the methods provided herein.

Hours		
2-48	Var. 682	
2-45	Var. 683	
2-42	Var. 684	
2-39	Var. 685	
2-36	Var. 686	10
2-33	Var. 687	
2-30	Var. 688	
2-27	Var. 689	
2-24	Var. 690	
2-22	Var. 691	
2-20	Var. 692	15
2-18	Var. 693	
2-16	Var. 694	
2-14	Var. 695	
2-12	Var. 696	
2-10	Var. 697	
2-8	Var. 698	
2-6	Var. 699	20
2-4	Var. 700	
3-90	Var. 701	
3-84	Var. 702	
3-78	Var. 703	
3-72	Var. 704	
3-66	Var. 705	25
3-60	Var. 706	
3-54	Var. 707	
3-48	Var. 708	
3-45	Var. 709	
3-42	Var. 710	
3-39	Var. 711	30
3-36	Var. 712	
3-33	Var. 713	
3-30	Var. 714	
3-27	Var. 715	
3-24	Var. 716	
3-22	Var. 717	35
3-20	Var. 718	
3-18	Var. 719	
3-16	Var. 720	
3-14	Var. 721	
3-12	Var. 722	
3-10	Var. 723	40
3-8	Var. 724	
3-6	Var. 725	
3-4	Var. 726	
4-90	Var. 727	
4-84	Var. 728	
4-78	Var. 729	
4-72	Var. 730	45
4-66	Var. 731	
4-60	Var. 732	
4-54	Var. 733	
4-48	Var. 734	
4-45	Var. 735	
4-42	Var. 736	50
4-39	Var. 737	
4-36	Var. 738	
4-33	Var. 739	
4-30	Var. 740	
4-27	Var. 741	
4-24	Var. 742	55
4-22	Var. 743	
4-20	Var. 744	
4-18	Var. 745	
4-16	Var. 746	
4-14	Var. 747	
4-12	Var. 748	
4-10	Var. 749	60
4-8	Var. 750	
4-6	Var. 751	
6-90	Var. 752	
6-84	Var. 753	
6-78	Var. 754	
6-72	Var. 755	65
6-66	Var. 756	

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TABLE 6-continued

Exemplary embodiments for the half-life of higher order rVWF multimers
found in the compositions and used in the methods provided herein.

Hours		
6-60	Var. 757	
6-54	Var. 758	
6-48	Var. 759	
6-45	Var. 760	
6-42	Var. 761	10
6-39	Var. 762	
6-36	Var. 763	
6-33	Var. 764	
6-30	Var. 765	
6-27	Var. 766	
6-24	Var. 767	15
6-22	Var. 768	
6-20	Var. 769	
6-18	Var. 770	
6-16	Var. 771	
6-14	Var. 772	
6-12	Var. 773	20
6-10	Var. 774	
6-8	Var. 775	
8-90	Var. 776	
8-84	Var. 777	
8-78	Var. 778	
8-72	Var. 779	
8-66	Var. 780	25
8-60	Var. 781	
8-54	Var. 782	
8-48	Var. 783	
8-45	Var. 784	
8-42	Var. 785	
8-39	Var. 786	30
8-36	Var. 787	
8-33	Var. 788	
8-30	Var. 789	
8-27	Var. 790	
8-24	Var. 791	
8-22	Var. 792	35
8-20	Var. 793	
8-18	Var. 794	
8-16	Var. 795	
8-14	Var. 796	
8-12	Var. 797	
8-10	Var. 798	40
10-90	Var. 799	
10-84	Var. 800	
10-78	Var. 801	
10-72	Var. 802	
10-66	Var. 803	
10-60	Var. 804	45
10-54	Var. 805	
10-48	Var. 806	
10-45	Var. 807	
10-42	Var. 808	
10-39	Var. 809	
10-36	Var. 810	
10-33	Var. 811	50
10-30	Var. 812	
10-27	Var. 813	
10-24	Var. 814	
10-22	Var. 815	
10-20	Var. 816	
10-18	Var. 817	55
10-16	Var. 818	
10-14	Var. 819	
10-12	Var. 820	
12-90	Var. 821	
12-84	Var. 822	
12-78	Var. 823	
12-72	Var. 824	60
12-66	Var. 825	
12-60	Var. 826	
12-54	Var. 827	
12-48	Var. 828	
12-45	Var. 829	
12-42	Var. 830	65
12-39	Var. 831	

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TABLE 6-continued

Exemplary embodiments for the half-life of higher order rVWF multimers found in the compositions and used in the methods provided herein.		
Hours		
12-36	Var. 832	5
12-33	Var. 833	
12-30	Var. 834	
12-27	Var. 835	
12-24	Var. 836	
12-22	Var. 837	10
12-20	Var. 838	
12-18	Var. 839	
12-16	Var. 840	
12-14	Var. 841	
14-90	Var. 842	15
14-84	Var. 843	
14-78	Var. 844	
14-72	Var. 845	
14-66	Var. 846	
14-60	Var. 847	20
14-54	Var. 848	
14-48	Var. 849	
14-45	Var. 850	
14-42	Var. 851	
14-39	Var. 852	25
14-36	Var. 853	
14-33	Var. 854	
14-30	Var. 855	
14-27	Var. 856	
14-24	Var. 857	30
14-22	Var. 858	
14-20	Var. 859	
14-18	Var. 860	
14-16	Var. 861	
16-90	Var. 862	35
16-84	Var. 863	
16-78	Var. 864	
16-72	Var. 865	
16-66	Var. 866	
16-60	Var. 867	40
16-54	Var. 868	
16-48	Var. 869	
16-45	Var. 870	
16-42	Var. 871	
16-39	Var. 872	45
16-36	Var. 873	
16-33	Var. 874	
16-30	Var. 875	
16-27	Var. 876	
16-24	Var. 877	50
16-22	Var. 878	
16-20	Var. 879	
16-18	Var. 880	
18-90	Var. 881	
18-84	Var. 882	55
18-78	Var. 883	
18-72	Var. 884	
18-66	Var. 885	
18-60	Var. 886	
18-54	Var. 887	60
18-48	Var. 888	
18-45	Var. 889	
18-42	Var. 890	
18-39	Var. 891	
18-36	Var. 892	65
18-33	Var. 893	
18-30	Var. 894	
18-27	Var. 895	
18-24	Var. 896	
18-22	Var. 897	60
18-20	Var. 898	
20-90	Var. 899	
20-84	Var. 900	
20-78	Var. 901	
20-72	Var. 902	65
20-66	Var. 903	
20-60	Var. 904	
20-54	Var. 905	
20-48	Var. 906	

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TABLE 6-continued

Exemplary embodiments for the half-life of higher order rVWF multimers found in the compositions and used in the methods provided herein.		
Hours		
20-45	Var. 907	5
20-42	Var. 908	
20-39	Var. 909	
20-36	Var. 910	
20-33	Var. 911	
20-30	Var. 912	10
20-27	Var. 913	
20-24	Var. 914	
20-22	Var. 915	
22-90	Var. 916	
22-84	Var. 917	15
22-78	Var. 918	
22-72	Var. 919	
22-66	Var. 920	
22-60	Var. 921	
22-54	Var. 922	20
22-48	Var. 923	
22-45	Var. 924	
22-42	Var. 925	
22-39	Var. 926	
22-36	Var. 927	25
22-33	Var. 928	
22-30	Var. 929	
22-27	Var. 930	
22-24	Var. 931	
24-90	Var. 932	30
24-84	Var. 933	
24-78	Var. 934	
24-72	Var. 935	
24-66	Var. 936	
24-60	Var. 937	35
24-54	Var. 938	
24-48	Var. 939	
24-45	Var. 940	
24-42	Var. 941	
24-39	Var. 942	40
24-36	Var. 943	
24-33	Var. 944	
24-30	Var. 945	
24-27	Var. 946	
27-90	Var. 947	45
27-84	Var. 948	
27-78	Var. 949	
27-72	Var. 950	
27-66	Var. 951	
27-60	Var. 952	50
27-54	Var. 953	
27-48	Var. 954	
30-90	Var. 955	
30-84	Var. 956	
30-78	Var. 957	55
30-72	Var. 958	
30-66	Var. 959	
30-60	Var. 960	
30-54	Var. 961	
30-48	Var. 962	60
30-45	Var. 963	
30-42	Var. 964	
30-39	Var. 965	
30-36	Var. 966	
30-33	Var. 967	65
33-90	Var. 968	
33-84	Var. 969	
33-78	Var. 970	
33-72	Var. 971	
33-66	Var. 972	60
33-60	Var. 973	
33-54	Var. 974	
33-48	Var. 975	
33-45	Var. 976	
33-42	Var. 977	65
33-39	Var. 978	
33-36	Var. 979	
36-90	Var. 980	
36-84	Var. 981	

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TABLE 6-continued

Exemplary embodiments for the half-life of higher order rVWF multimers found in the compositions and used in the methods provided herein.

Hours	
36-78	Var. 982
36-72	Var. 983
36-66	Var. 984
36-60	Var. 985
36-54	Var. 986
36-48	Var. 987
36-45	Var. 988
36-42	Var. 989
36-39	Var. 990
39-90	Var. 991
39-84	Var. 992
39-78	Var. 993
39-72	Var. 994
39-66	Var. 995
39-60	Var. 996
39-54	Var. 997
39-48	Var. 998
39-45	Var. 999
39-42	Var. 1000
42-90	Var. 1001
42-84	Var. 1002
42-78	Var. 1003
42-72	Var. 1004
42-66	Var. 1005
42-60	Var. 1006
42-54	Var. 1007
42-48	Var. 1008
42-45	Var. 1009
45-90	Var. 1010
45-84	Var. 1011
45-78	Var. 1012
45-72	Var. 1013
45-66	Var. 1014
45-60	Var. 1015
45-54	Var. 1016
45-48	Var. 1017
48-90	Var. 1018
48-84	Var. 1019
48-78	Var. 1020
48-72	Var. 1021
48-66	Var. 1022
48-60	Var. 1023
48-54	Var. 1024
54-90	Var. 1025
54-84	Var. 1026
54-78	Var. 1027
54-72	Var. 1028
54-66	Var. 1029
54-60	Var. 1030
60-90	Var. 1031
60-84	Var. 1032
60-78	Var. 1033
60-72	Var. 1034
60-66	Var. 1035
66-90	Var. 1036
66-84	Var. 1037
66-78	Var. 1038
66-72	Var. 1039
72-90	Var. 1040
72-84	Var. 1041
72-78	Var. 1042
78-90	Var. 1043
78-84	Var. 1044
84-90	Var. 1045

Var. = Variation

In further aspects, rVWF of use in the present invention increases stability of plasma FVIII, which, as will be appreciated, may include pdFVII or rFVIII which has been administered to the patient or it may include FVIII endogenous to the patient, or any combination thereof. For example, as shown in FIG. 22, the half-life of plasma FVIII is increased in VWD patients receiving rVWF in combination with rFVIII as compared to patients receiving FVIII (i.e., Advate) alone. In

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further embodiments, rVWF increases half-life of FVIII by about 1.5-5-fold as compared to the half-life seen with patients receiving FVIII alone. In still further embodiments, rVWF increases half-life of FVIII by about 1.0-4.5, 1.5-4.0, 2.0-3.5, 2.5-3.0 fold. In one embodiment, administration of rVWF increases the stability of plasma FVIII, as compared to the administration of plasma-derived VWF, by an amount selected from variations 1046 to 1089 found in Table 7. In a specific embodiment, administration of a rVWF/FVIII complex increases the stability of plasma FVIII, as compared to the administration of plasma-derived VWF, by an amount selected from variations 1046 to 1089 found in Table 7.

TABLE 7

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.

	Increase in plasma FVIII half-life	
	at least 1.5-fold	Var. 1046
	at least 2.0-fold	Var. 1047
25	at least 2.5-fold	Var. 1048
	at least 3.0-fold	Var. 1049
	at least 3.5-fold	Var. 1050
30	at least 4.0-fold	Var. 1051
	at least 4.5 fold	Var. 1052
	at least 5.0-fold	Var. 1053
35	1.5-fold	Var. 1054
	2.0-fold	Var. 1055
	2.5-fold	Var. 1056
40	3.0-fold	Var. 1057
	3.5-fold	Var. 1058
	4.0-fold	Var. 1059
45	4.5-fold	Var. 1060
	5.0-fold	Var. 1061
	1.5-5.0 fold	Var. 1062
50	1.5-4.5 fold	Var. 1063
	1.5-4.0 fold	Var. 1064
	1.5-3.5 fold	Var. 1065
55	1.5-3.0 fold	Var. 1066
	1.5-2.5 fold	Var. 1067
	1.5-2.0 fold	Var. 1068
60	2-5.0 fold	Var. 1069
	2-4.5 fold	Var. 1070
	2-4.0 fold	Var. 1071
	2-3.5 fold	Var. 1072
65	2-3.0 fold	Var.

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TABLE 7-continued

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.			5
Increase in plasma FVIII half-life			
	1073		10
2-2.5 fold	Var.		
	1074		
2.5-5.0 fold	Var.		15
	1075		
2.5-4.5 fold	Var.		
	1076		20
2.5-4.0 fold	Var.		
	1077		
2.5-3.5 fold	Var.		25
	1078		
2.5-3.0 fold	Var.		
	1079		30
3-5.0 fold	Var.		
	1080		
3-4.5 fold	Var.		35
	1081		
3-4.0 fold	Var.		
	1082		40
3-3.5 fold	Var.		
	1083		
3.5-5.0 fold	Var.		45
	1084		
3.5-4.5 fold	Var.		
	1085		50
3.5-4.0 fold	Var.		
	1086		
4-5.0 fold	Var.		55
	1087		
4-4.5 fold	Var.		
	1088		60
4.5-5.0 fold	Var.		
	1089		

Var. = Variation

In still further embodiments, the increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF.

In one embodiment, the increase in the mean residence time (MRT) plasma FVIII is maintained for a time selected from variations 1090 to 1299 found in Table 8, after administration of rVWF. In a specific embodiment, the increase in the half life of plasma FVIII is maintained for a time selected from variations 1090 to 1299 found in Table 8, after administration of a rVWF/FVIII complex.

TABLE 8

Exemplary embodiments for the time plasma FVIII stability is maintained after administration of rVWF and rVWF/FVIII complexes.			55
Hours			
at least 6	Var. 1090		60
at least 12	Var. 1091		
at least 18	Var. 1092		
at least 24	Var. 1093		
at least 30	Var. 1094		
at least 36	Var. 1095		
at least 42	Var. 1096		
at least 48	Var. 1097		65
at least 54	Var. 1098		
at least 60	Var. 1099		

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TABLE 8-continued

Exemplary embodiments for the time plasma FVIII stability is maintained after administration of rVWF and rVWF/FVIII complexes.			5
Hours			
at least 66	Var. 1100		60
at least 72	Var. 1101		
at least 78	Var. 1102		
at least 84	Var. 1103		
at least 90	Var. 1104		
at least 96	Var. 1105		
at least 102	Var. 1106		
at least 108	Var. 1107		65
at least 114	Var. 1108		
at least 120	Var. 1109		
6-120	Var. 1110		
6-114	Var. 1111		
6-108	Var. 1112		
6-102	Var. 1113		
6-96	Var. 1114		70
6-90	Var. 1115		
6-84	Var. 1116		
6-78	Var. 1117		
6-72	Var. 1118		
6-66	Var. 1119		
6-60	Var. 1120		
6-54	Var. 1121		75
6-48	Var. 1122		
6-42	Var. 1123		
6-36	Var. 1124		
6-30	Var. 1125		
6-24	Var. 1126		
6-18	Var. 1127		
6-12	Var. 1128		80
12-120	Var. 1129		
12-114	Var. 1130		
12-108	Var. 1131		
12-102	Var. 1132		
12-96	Var. 1133		
12-90	Var. 1134		
12-84	Var. 1135		85
12-78	Var. 1136		
12-72	Var. 1137		
12-66	Var. 1138		
12-60	Var. 1139		
12-54	Var. 1140		
12-48	Var. 1141		
12-42	Var. 1142		90
12-36	Var. 1143		
12-30	Var. 1144		
12-24	Var. 1145		
12-18	Var. 1146		
18-120	Var. 1147		
18-114	Var. 1148		
18-108	Var. 1149		95
18-102	Var. 1150		
18-96	Var. 1151		
18-90	Var. 1152		
18-84	Var. 1153		
18-78	Var. 1154		
18-72	Var. 1155		
18-66	Var. 1156		100
18-60	Var. 1157		
18-54	Var. 1158		
18-48	Var. 1159		
18-42	Var. 1160		
18-36	Var. 1161		
18-30	Var. 1162		
18-24	Var. 1163		105
24-120	Var. 1164		
24-114	Var. 1165		
24-108	Var. 1166		
24-102	Var. 1167		
24-96	Var. 1168		
24-90	Var. 1169		
24-84	Var. 1170		110
24-78	Var. 1171		
24-72	Var. 1172		
24-66	Var. 1173		
24-60	Var. 1174		

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TABLE 8-continued

Exemplary embodiments for the time plasma FVIII stability is maintained after administration of rVWF and rVWF/FVIII complexes.		
Hours		
24-54	Var. 1175	
24-48	Var. 1176	
24-42	Var. 1177	
24-36	Var. 1178	
24-30	Var. 1179	
30-120	Var. 1180	
30-114	Var. 1181	
30-108	Var. 1182	
30-102	Var. 1183	
30-96	Var. 1184	
30-90	Var. 1185	
30-84	Var. 1186	
30-78	Var. 1187	
30-72	Var. 1188	
30-66	Var. 1189	
30-60	Var. 1190	
30-54	Var. 1191	
30-48	Var. 1192	
30-42	Var. 1193	
30-36	Var. 1194	
36-120	Var. 1195	
36-114	Var. 1196	
36-108	Var. 1197	
36-102	Var. 1198	
36-96	Var. 1199	
36-90	Var. 1200	
36-84	Var. 1201	
36-78	Var. 1202	
36-72	Var. 1203	
36-66	Var. 1204	
36-60	Var. 1205	
36-54	Var. 1206	
36-48	Var. 1207	
36-42	Var. 1208	
42-120	Var. 1209	
42-114	Var. 1210	
42-108	Var. 1211	
42-102	Var. 1212	
42-96	Var. 1213	
42-90	Var. 1214	
42-84	Var. 1215	
42-78	Var. 1216	
42-72	Var. 1217	
42-66	Var. 1218	
42-60	Var. 1219	
42-54	Var. 1220	
42-48	Var. 1221	
48-120	Var. 1222	
48-114	Var. 1223	
48-108	Var. 1224	
48-102	Var. 1225	
48-96	Var. 1226	
48-90	Var. 1227	
48-84	Var. 1228	
48-78	Var. 1229	
48-72	Var. 1230	
48-66	Var. 1231	
48-60	Var. 1232	
48-54	Var. 1233	
54-120	Var. 1234	
54-114	Var. 1235	
54-108	Var. 1236	
54-102	Var. 1237	
54-96	Var. 1238	
54-90	Var. 1239	
54-84	Var. 1240	
54-78	Var. 1241	
54-72	Var. 1242	
54-66	Var. 1243	
54-60	Var. 1244	
60-120	Var. 1245	
60-114	Var. 1246	
60-108	Var. 1247	
60-102	Var. 1248	
60-96	Var. 1249	

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TABLE 8-continued

Exemplary embodiments for the time plasma FVIII stability is maintained after administration of rVWF and rVWF/FVIII complexes.		
Hours		
60-90	Var. 1250	
60-84	Var. 1251	
60-78	Var. 1252	
60-72	Var. 1253	
60-66	Var. 1254	
66-120	Var. 1255	
66-114	Var. 1256	
66-108	Var. 1257	
66-102	Var. 1258	
66-96	Var. 1259	
66-90	Var. 1260	
66-84	Var. 1261	
66-78	Var. 1262	
66-72	Var. 1263	
72-120	Var. 1264	
72-114	Var. 1265	
72-108	Var. 1266	
72-102	Var. 1267	
72-96	Var. 1268	
72-90	Var. 1269	
72-84	Var. 1270	
72-78	Var. 1271	
78-120	Var. 1272	
78-114	Var. 1273	
78-108	Var. 1274	
78-102	Var. 1275	
78-96	Var. 1276	
78-90	Var. 1277	
78-84	Var. 1278	
84-120	Var. 1279	
84-114	Var. 1280	
84-108	Var. 1281	
84-102	Var. 1282	
84-96	Var. 1283	
84-90	Var. 1284	
90-120	Var. 1285	
90-114	Var. 1286	
90-108	Var. 1287	
90-102	Var. 1288	
90-96	Var. 1289	
96-120	Var. 1290	
96-114	Var. 1291	
96-108	Var. 1292	
96-102	Var. 1293	
102-120	Var. 1294	
102-114	Var. 1295	
102-108	Var. 1296	
108-120	Var. 1297	
108-114	Var. 1298	
114-120	Var. 1299	

Var. = Variation

In further aspects, the rVWF of the invention shows an increased effect on the stability of FVIII as compared to the effect of pdVWF. For example, as shown in FIG. 20, average FVIII half-life was increased by rVWF by 5.2 hours over the half-life for patients receiving pdVWF. In further embodiments, rVWF increases average FVIII half-life by about 1-15, 2-14, 3-13, 4-12, 5-11, 6-10, 5-9, 6-8 hours. In still further embodiments, rVWF increases FVIII half-life by about 10% to about 75% as compared to pdVWF. In yet further embodiments, rVWF increases FVIII half-life by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In certain embodiments, the administration of rVWF increases the half life of FVIII by an amount selected from variations 1300 to 1643 found in Table 9, as compared to administration of plasma-derived VWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further

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embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF.

TABLE 9

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.	
Increase in half life	
at least 1 hr	Var. 1300
at least 2 hr	Var. 1301
at least 3 hr	Var. 1302
at least 4 hr	Var. 1303
at least 5 hr	Var. 1304
at least 6 hr	Var. 1305
at least 7 hr	Var. 1306
at least 8 hr	Var. 1307
at least 9 hr	Var. 1308
at least 10 hr	Var. 1309
at least 11 hr	Var. 1310
at least 12 hr	Var. 1311
at least 13 hr	Var. 1312
at least 14 hr	Var. 1313
at least 15 hr	Var. 1314
1 hr	Var. 1315
2 hr	Var. 1316
3 hr	Var. 1317
4 hr	Var. 1318
5 hr	Var. 1319
6 hr	Var. 1320
7 hr	Var. 1321
8 hr	Var. 1322
9 hr	Var. 1323
10 hr	Var. 1324
11 hr	Var. 1325
12 hr	Var. 1326
13 hr	Var. 1327
14 hr	Var. 1328
15 hr	Var. 1329
1-15 hr	Var. 1330
1-14 hr	Var. 1331
1-13 hr	Var. 1332
1-12 hr	Var. 1333
1-11 hr	Var. 1334
1-10 hr	Var. 1335
1-9 hr	Var. 1336
1-8 hr	Var. 1337
1-7 hr	Var. 1338
1-6 hr	Var. 1339
1-5 hr	Var. 1340
1-4 hr	Var. 1341
1-3 hr	Var. 1342
1-2 hr	Var. 1343
2-15 hr	Var. 1344
2-14 hr	Var. 1345
2-13 hr	Var. 1346
2-12 hr	Var. 1347
2-11 hr	Var. 1348
2-10 hr	Var. 1349
2-9 hr	Var. 1350
2-8 hr	Var. 1351
2-7 hr	Var. 1352
2-6 hr	Var. 1353
2-5 hr	Var. 1354
2-4 hr	Var. 1355
2-3 hr	Var. 1356
3-15 hr	Var. 1357
3-14 hr	Var. 1358
3-13 hr	Var. 1359
3-12 hr	Var. 1360
3-11 hr	Var. 1361
3-10 hr	Var. 1362
3-9 hr	Var. 1363
3-8 hr	Var. 1364
3-7 hr	Var. 1365
3-6 hr	Var. 1366
3-5 hr	Var. 1367
3-4 hr	Var. 1368

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TABLE 9-continued

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.

Increase in half life	
4-15 hr	Var. 1369
4-14 hr	Var. 1370
4-13 hr	Var. 1371
4-12 hr	Var. 1372
4-11 hr	Var. 1373
4-10 hr	Var. 1374
4-9 hr	Var. 1375
4-8 hr	Var. 1376
4-7 hr	Var. 1377
4-6 hr	Var. 1378
4-5 hr	Var. 1379
5-15 hr	Var. 1380
5-14 hr	Var. 1381
5-13 hr	Var. 1382
5-12 hr	Var. 1383
5-11 hr	Var. 1384
5-10 hr	Var. 1385
5-9 hr	Var. 1386
5-8 hr	Var. 1387
5-7 hr	Var. 1388
5-6 hr	Var. 1389
6-15 hr	Var. 1390
6-14 hr	Var. 1391
6-13 hr	Var. 1392
6-12 hr	Var. 1393
6-11 hr	Var. 1394
6-10 hr	Var. 1395
6-9 hr	Var. 1396
6-8 hr	Var. 1397
6-7 hr	Var. 1398
7-15 hr	Var. 1399
7-14 hr	Var. 1400
7-13 hr	Var. 1401
7-12 hr	Var. 1402
7-11 hr	Var. 1403
7-10 hr	Var. 1404
7-9 hr	Var. 1405
7-8 hr	Var. 1406
8-15 hr	Var. 1407
8-14 hr	Var. 1408
8-13 hr	Var. 1409
8-12 hr	Var. 1410
8-11 hr	Var. 1411
8-10 hr	Var. 1412
8-9 hr	Var. 1413
9-15 hr	Var. 1414
9-14 hr	Var. 1415
9-13 hr	Var. 1416
9-12 hr	Var. 1417
9-11 hr	Var. 1418
9-10 hr	Var. 1419
10-15 hr	Var. 1420
10-14 hr	Var. 1421
10-13 hr	Var. 1422
10-12 hr	Var. 1423
10-11 hr	Var. 1424
11-15 hr	Var. 1425
11-14 hr	Var. 1426
11-13 hr	Var. 1427
11-12 hr	Var. 1428
12-15 hr	Var. 1429
12-14 hr	Var. 1430
12-13 hr	Var. 1431
13-15 hr	Var. 1432
13-14 hr	Var. 1433
14-15 hr	Var. 1434
at least 10%	Var. 1435
at least 15%	Var. 1436
at least 20%	Var. 1437
at least 25%	Var. 1438
at least 30%	Var. 1439
at least 35%	Var. 1440
at least 40%	Var. 1441
at least 45%	Var. 1442

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TABLE 9-continued

Exemplary embodiments of the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.	
Increase in half life	
at least 50%	Var. 1443
at least 55%	Var. 1444
at least 60%	Var. 1445
at least 65%	Var. 1446
at least 70%	Var. 1447
at least 75%	Var. 1448
at least 80%	Var. 1449
at least 85%	Var. 1450
at least 90%	Var. 1451
at least 95%	Var. 1452
at least 100%	Var. 1453
10%	Var. 1454
15%	Var. 1455
20%	Var. 1456
25%	Var. 1457
30%	Var. 1458
35%	Var. 1459
40%	Var. 1460
45%	Var. 1461
50%	Var. 1462
55%	Var. 1463
60%	Var. 1464
65%	Var. 1465
70%	Var. 1466
75%	Var. 1467
80%	Var. 1468
85%	Var. 1469
90%	Var. 1470
95%	Var. 1471
100%	Var. 1472
10-100%	Var. 1473
10-95%	Var. 1474
10-90%	Var. 1475
10-85%	Var. 1476
10-80%	Var. 1477
10-75%	Var. 1478
10-70%	Var. 1479
10-65%	Var. 1480
10-60%	Var. 1481
10-55%	Var. 1482
10-50%	Var. 1483
10-45%	Var. 1484
10-40%	Var. 1485
10-35%	Var. 1486
10-30%	Var. 1487
10-25%	Var. 1488
10-20%	Var. 1489
10-15%	Var. 1490
15-100%	Var. 1491
15-95%	Var. 1492
15-90%	Var. 1493
15-85%	Var. 1494
15-80%	Var. 1495
15-75%	Var. 1496
15-70%	Var. 1497
15-65%	Var. 1498
15-60%	Var. 1499
15-55%	Var. 1500
15-50%	Var. 1501
15-45%	Var. 1502
15-40%	Var. 1503
15-35%	Var. 1504
15-30%	Var. 1505
15-25%	Var. 1506
15-20%	Var. 1507
20-100%	Var. 1508
20-95%	Var. 1509
20-90%	Var. 1510
20-85%	Var. 1511
20-80%	Var. 1512
20-75%	Var. 1513
20-70%	Var. 1514
20-65%	Var. 1515
20-60%	Var. 1516

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TABLE 9-continued

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.	
Increase in half life	
20-55%	Var. 1517
20-50%	Var. 1518
20-45%	Var. 1519
20-40%	Var. 1520
20-35%	Var. 1521
20-30%	Var. 1522
20-25%	Var. 1523
25-100%	Var. 1524
25-95%	Var. 1525
25-90%	Var. 1526
25-85%	Var. 1527
25-80%	Var. 1528
25-75%	Var. 1529
25-70%	Var. 1530
25-65%	Var. 1531
25-60%	Var. 1532
25-55%	Var. 1533
25-50%	Var. 1534
25-45%	Var. 1535
25-40%	Var. 1536
25-35%	Var. 1537
25-30%	Var. 1538
30-100%	Var. 1539
30-95%	Var. 1540
30-90%	Var. 1541
30-85%	Var. 1542
30-80%	Var. 1543
30-75%	Var. 1544
30-70%	Var. 1545
30-65%	Var. 1546
30-60%	Var. 1547
30-55%	Var. 1548
30-50%	Var. 1549
30-45%	Var. 1550
30-40%	Var. 1551
30-35%	Var. 1552
35-100%	Var. 1553
35-95%	Var. 1554
35-90%	Var. 1555
35-85%	Var. 1556
35-80%	Var. 1557
35-75%	Var. 1558
35-70%	Var. 1559
35-65%	Var. 1560
35-60%	Var. 1561
35-55%	Var. 1562
35-50%	Var. 1563
35-45%	Var. 1564
35-40%	Var. 1565
40-100%	Var. 1566
40-95%	Var. 1567
40-90%	Var. 1568
40-85%	Var. 1569
40-80%	Var. 1570
40-75%	Var. 1571
40-70%	Var. 1572
40-65%	Var. 1573
40-60%	Var. 1574
40-55%	Var. 1575
40-50%	Var. 1576
40-45%	Var. 1577
45-100%	Var. 1578
45-95%	Var. 1579
45-90%	Var. 1580
45-85%	Var. 1581
45-80%	Var. 1582
45-75%	Var. 1583
45-70%	Var. 1584
45-65%	Var. 1585
45-60%	Var. 1586
45-55%	Var. 1587
45-50%	Var. 1588
50-100%	Var. 1589
50-95%	Var. 1590

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TABLE 9-continued

Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.	
Increase in half life	
50-90%	Var. 1591
50-85%	Var. 1592
50-80%	Var. 1593
50-75%	Var. 1594
50-70%	Var. 1595
50-65%	Var. 1596
50-60%	Var. 1597
50-55%	Var. 1598
55-100%	Var. 1599
55-95%	Var. 1600
55-90%	Var. 1601
55-85%	Var. 1602
55-80%	Var. 1603
55-75%	Var. 1604
55-70%	Var. 1605
55-65%	Var. 1606
55-60%	Var. 1607
60-100%	Var. 1608
60-95%	Var. 1609
60-90%	Var. 1610
60-85%	Var. 1611
60-80%	Var. 1612
60-75%	Var. 1613
60-70%	Var. 1614
60-65%	Var. 1615
65-100%	Var. 1616
65-95%	Var. 1617
65-90%	Var. 1618
65-85%	Var. 1619
65-80%	Var. 1620
65-75%	Var. 1621
65-70%	Var. 1622
70-100%	Var. 1623
70-95%	Var. 1624
70-90%	Var. 1625
70-85%	Var. 1626
70-80%	Var. 1627
70-75%	Var. 1628
75-100%	Var. 1629
75-95%	Var. 1630
75-90%	Var. 1631
75-85%	Var. 1632
75-80%	Var. 1633
80-100%	Var. 1634
80-95%	Var. 1635
80-90%	Var. 1636
80-85%	Var. 1637
85-100%	Var. 1638
85-95%	Var. 1639
85-90%	Var. 1640
90-100%	Var. 1641
90-95%	Var. 1642
95%-100%	Var. 1643

Var. = Variation

In still further aspects and in accordance with any of the above, the stabilization of FVIII activity by rVWF as compared to pdVWF can be measured by metrics in addition to FVIII half-life, including mean residence time (MRT) and area under curve (AUC). In exemplary embodiments, rVWF increases MRT by about 1-15 hours as compared to pdVWF. In further embodiments, rVWF increases MRT by about 1-25, 2-20, 3-15, 4-10, 5-9, 6-8 hours as compared to pdVWF. In still further embodiments, rVWF increases FVIII MRT by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In certain embodiments, the administration of rVWF increases the MRT of FVIII by an amount

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selected from variations 1644 to 1987 found in Table 10, as compared to administration of plasma-derived VWF.

In yet further embodiments, the increase in MRT is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. In certain embodiments, the increase in MRT of FVIII caused by administration of rVWF is maintained for a time selected from variations 1090 to 1299 found in Table 8.

TABLE 10

Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.	
Increase in half life	
10	at least 1 hr Var. 1644
	at least 2 hr Var. 1645
	at least 3 hr Var. 1646
	at least 4 hr Var. 1647
	at least 5 hr Var. 1648
15	at least 6 hr Var. 1649
	at least 7 hr Var. 1650
	at least 8 hr Var. 1651
	at least 9 hr Var. 1652
	at least 10 hr Var. 1653
20	at least 11 hr Var. 1654
	at least 12 hr Var. 1655
	at least 13 hr Var. 1656
	at least 14 hr Var. 1657
	at least 15 hr Var. 1658
25	1 hr Var. 1659
	2 hr Var. 1660
	3 hr Var. 1661
	4 hr Var. 1662
	5 hr Var. 1663
30	6 hr Var. 1664
	7 hr Var. 1665
	8 hr Var. 1666
	9 hr Var. 1667
	10 hr Var. 1668
35	11 hr Var. 1669
	12 hr Var. 1670
	13 hr Var. 1671
	14 hr Var. 1672
	15 hr Var. 1673
40	1-15 hr Var. 1674
	1-14 hr Var. 1675
	1-13 hr Var. 1676
	1-12 hr Var. 1677
	1-11 hr Var. 1678
45	1-10 hr Var. 1679
	1-9 hr Var. 1680
	1-8 hr Var. 1681
	1-7 hr Var. 1682
	1-6 hr Var. 1683
50	1-5 hr Var. 1684
	1-4 hr Var. 1685
	1-3 hr Var. 1686
	1-2 hr Var. 1687
	2-15 hr Var. 1688
55	2-14 hr Var. 1689
	2-13 hr Var. 1690
	2-12 hr Var. 1691
	2-11 hr Var. 1692
	2-10 hr Var. 1693
60	2-9 hr Var. 1694
	2-8 hr Var. 1695
	2-7 hr Var. 1696
	2-6 hr Var. 1697
	2-5 hr Var. 1698
65	2-4 hr Var. 1699
	2-3 hr Var. 1700
	3-15 hr Var. 1701
	3-14 hr Var. 1702
	3-13 hr Var. 1703
	3-12 hr Var. 1704

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TABLE 10-continued

Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.	
Increase in half life	
3-11 hr	Var. 1705
3-10 hr	Var. 1706
3-9 hr	Var. 1707
3-8 hr	Var. 1708
3-7 hr	Var. 1709
3-6 hr	Var. 1710
3-5 hr	Var. 1711
3-4 hr	Var. 1712
4-15 hr	Var. 1713
4-14 hr	Var. 1714
4-13 hr	Var. 1715
4-12 hr	Var. 1716
4-11 hr	Var. 1717
4-10 hr	Var. 1718
4-9 hr	Var. 1719
4-8 hr	Var. 1720
4-7 hr	Var. 1721
4-6 hr	Var. 1722
4-5 hr	Var. 1723
5-15 hr	Var. 1724
5-14 hr	Var. 1725
5-13 hr	Var. 1726
5-12 hr	Var. 1727
5-11 hr	Var. 1728
5-10 hr	Var. 1729
5-9 hr	Var. 1730
5-8 hr	Var. 1731
5-7 hr	Var. 1732
5-6 hr	Var. 1733
6-15 hr	Var. 1734
6-14 hr	Var. 1735
6-13 hr	Var. 1736
6-12 hr	Var. 1737
6-11 hr	Var. 1738
6-10 hr	Var. 1739
6-9 hr	Var. 1740
6-8 hr	Var. 1741
6-7 hr	Var. 1742
7-15 hr	Var. 1743
7-14 hr	Var. 1744
7-13 hr	Var. 1745
7-12 hr	Var. 1746
7-11 hr	Var. 1747
7-10 hr	Var. 1748
7-9 hr	Var. 1749
7-8 hr	Var. 1750
8-15 hr	Var. 1751
8-14 hr	Var. 1752
8-13 hr	Var. 1753
8-12 hr	Var. 1754
8-11 hr	Var. 1755
8-10 hr	Var. 1756
8-9 hr	Var. 1757
9-15 hr	Var. 1758
9-14 hr	Var. 1759
9-13 hr	Var. 1760
9-12 hr	Var. 1761
9-11 hr	Var. 1762
9-10 hr	Var. 1763
10-15 hr	Var. 1764
10-14 hr	Var. 1765
10-13 hr	Var. 1766
10-12 hr	Var. 1767
10-11 hr	Var. 1768
11-15 hr	Var. 1769
11-14 hr	Var. 1770
11-13 hr	Var. 1771
11-12 hr	Var. 1772
12-15 hr	Var. 1773
12-14 hr	Var. 1774
12-13 hr	Var. 1775
13-15 hr	Var. 1776

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TABLE 10-continued

Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.	
Increase in half life	
13-14 hr	Var. 1777
14-15 hr	Var. 1778
at least 10%	Var. 1779
at least 15%	Var. 1780
at least 20%	Var. 1781
at least 25%	Var. 1782
at least 30%	Var. 1783
at least 35%	Var. 1784
at least 40%	Var. 1785
at least 45%	Var. 1786
at least 50%	Var. 1787
at least 55%	Var. 1788
at least 60%	Var. 1789
at least 65%	Var. 1790
at least 70%	Var. 1791
at least 75%	Var. 1792
at least 80%	Var. 1793
at least 85%	Var. 1794
at least 90%	Var. 1795
at least 95%	Var. 1796
at least 100%	Var. 1797
10%	Var. 1798
15%	Var. 1799
20%	Var. 1800
25%	Var. 1801
30%	Var. 1802
35%	Var. 1803
40%	Var. 1804
45%	Var. 1805
50%	Var. 1806
55%	Var. 1807
60%	Var. 1808
65%	Var. 1809
70%	Var. 1810
75%	Var. 1811
80%	Var. 1812
85%	Var. 1813
90%	Var. 1814
95%	Var. 1815
100%	Var. 1816
10-100%	Var. 1817
10-95%	Var. 1818
10-90%	Var. 1819
10-85%	Var. 1820
10-80%	Var. 1821
10-75%	Var. 1822
10-70%	Var. 1823
10-65%	Var. 1824
10-60%	Var. 1825
10-55%	Var. 1826
10-50%	Var. 1827
10-45%	Var. 1828
10-40%	Var. 1829
10-35%	Var. 1830
10-30%	Var. 1831
10-25%	Var. 1832
10-20%	Var. 1833
10-15%	Var. 1834
15-100%	Var. 1835
15-95%	Var. 1836
15-90%	Var. 1837
15-85%	Var. 1838
15-80%	Var. 1839
15-75%	Var. 1840
15-70%	Var. 1841
15-65%	Var. 1842
15-60%	Var. 1843
15-55%	Var. 1844
15-50%	Var. 1845
15-45%	Var. 1846
15-40%	Var. 1847
15-35%	Var. 1848

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TABLE 10-continued

Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.		
Increase in half life		
15-30%	Var. 1849	5
15-25%	Var. 1850	
15-20%	Var. 1851	
20-100%	Var. 1852	
20-95%	Var. 1853	
20-90%	Var. 1854	10
20-85%	Var. 1855	
20-80%	Var. 1856	
20-75%	Var. 1857	
20-70%	Var. 1858	
20-65%	Var. 1859	15
20-60%	Var. 1860	
20-55%	Var. 1861	
20-50%	Var. 1862	
20-45%	Var. 1863	
20-40%	Var. 1864	20
20-35%	Var. 1865	
20-30%	Var. 1866	
20-25%	Var. 1867	
25-100%	Var. 1868	
25-95%	Var. 1869	25
25-90%	Var. 1870	
25-85%	Var. 1871	
25-80%	Var. 1872	
25-75%	Var. 1873	
25-70%	Var. 1874	30
25-65%	Var. 1875	
25-60%	Var. 1876	
25-55%	Var. 1877	
25-50%	Var. 1878	
25-45%	Var. 1879	35
25-40%	Var. 1880	
25-35%	Var. 1881	
25-30%	Var. 1882	
30-100%	Var. 1883	
30-95%	Var. 1884	40
30-90%	Var. 1885	
30-85%	Var. 1886	
30-80%	Var. 1887	
30-75%	Var. 1888	
30-70%	Var. 1889	45
30-65%	Var. 1890	
30-60%	Var. 1891	
30-55%	Var. 1892	
30-50%	Var. 1893	
30-45%	Var. 1894	50
30-40%	Var. 1895	
30-35%	Var. 1896	
35-100%	Var. 1897	
35-95%	Var. 1898	
35-90%	Var. 1899	55
35-85%	Var. 1900	
35-80%	Var. 1901	
35-75%	Var. 1902	
35-70%	Var. 1903	
35-65%	Var. 1904	60
35-60%	Var. 1905	
35-55%	Var. 1906	
35-50%	Var. 1907	
35-45%	Var. 1908	
35-40%	Var. 1909	65
40-100%	Var. 1910	
40-95%	Var. 1911	
40-90%	Var. 1912	
40-85%	Var. 1913	
40-80%	Var. 1914	
40-75%	Var. 1915	
40-70%	Var. 1916	
40-65%	Var. 1917	
40-60%	Var. 1918	
40-55%	Var. 1919	
40-50%	Var. 1920	

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TABLE 10-continued

Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.		
Increase in half life		
40-45%	Var. 1921	5
45-100%	Var. 1922	
45-95%	Var. 1923	
45-90%	Var. 1924	
45-85%	Var. 1925	
45-80%	Var. 1926	10
45-75%	Var. 1927	
45-70%	Var. 1928	
45-65%	Var. 1929	
45-60%	Var. 1930	
45-55%	Var. 1931	15
45-50%	Var. 1932	
50-100%	Var. 1933	
50-95%	Var. 1934	
50-90%	Var. 1935	
50-85%	Var. 1936	20
50-80%	Var. 1937	
50-75%	Var. 1938	
50-70%	Var. 1939	
50-65%	Var. 1940	
50-60%	Var. 1941	25
50-55%	Var. 1942	
55-100%	Var. 1943	
55-95%	Var. 1944	
55-90%	Var. 1945	
55-85%	Var. 1946	30
55-80%	Var. 1947	
55-75%	Var. 1948	
55-70%	Var. 1949	
55-65%	Var. 1950	
55-60%	Var. 1951	35
60-100%	Var. 1952	
60-95%	Var. 1953	
60-90%	Var. 1954	
60-85%	Var. 1955	
60-80%	Var. 1956	40
60-75%	Var. 1957	
60-70%	Var. 1958	
60-65%	Var. 1959	
65-100%	Var. 1960	
65-95%	Var. 1961	45
65-90%	Var. 1962	
65-85%	Var. 1963	
65-80%	Var. 1964	
65-75%	Var. 1965	
65-70%	Var. 1966	50
70-100%	Var. 1967	
70-95%	Var. 1968	
70-90%	Var. 1969	
70-85%	Var. 1970	
70-80%	Var. 1971	55
70-75%	Var. 1972	
75-100%	Var. 1973	
75-95%	Var. 1974	
75-90%	Var. 1975	
75-85%	Var. 1976	60
75-80%	Var. 1977	
80-100%	Var. 1978	
80-95%	Var. 1979	
80-90%	Var. 1980	
80-85%	Var. 1981	65
85-100%	Var. 1982	
85-95%	Var. 1983	
85-90%	Var. 1984	
90-100%	Var. 1985	
90-95%	Var. 1986	
95%-100%	Var. 1987	

Var. = Variation

Further exemplary differences between pdVWF and rVWF are provided in the following table:

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pdVWF	rVWF
Synthesized in endothelial cells and megakaryocytes	Expressed in CHO cells
Post-translational modification of propeptide removal occurs intracellularly: during passage of the protein to the Golgi and post-Golgi compartments	Propeptide removal mediated in vitro through exposure of the pro-VWF to recombinant Furin
Glycosylation/ABO blood group glycans present	Fully glycosylated/ABO blood group glycans absent
Consists of VWF subunits that have been exposed to plasma ADAMTS13	No exposure to ADAMTS13
→ Ultra-large VWF multimers absent	→ Intact VWF subunits
→ Subunits cleaved at TYR ¹⁶⁰⁵ .MET ¹⁶⁰⁶	→ Ultra-large VWF multimers present
	→ Subunit cleavage occurs upon ADAMTS13 exposure
Plasma-derived VWF concentrates contain other proteins incl. ADAMTS13, hemagglutinins	Higher specific activity than pdVWF

In some embodiments, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) is between 3:1 and 1:5. In further embodiments, the ratio is between 2:1 and 1:4. In still further embodiments, the ratio is between 5:2 and 1:4. In further embodiments, the ratio is between 3:2 and 1:3. In still further embodiments, the ratio is about 1:1, 1:2, 1:3, 1:4, 1:5, 2:1, 2:3, 2:4, 2:5, 3:1, 3:2, 3:4, or 3:5. In further embodiments, the ratio is between 1:1 and 1:2. In yet further embodiments, the ratio is 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, or 2:1. In certain embodiments, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in a composition useful for a method described herein is selected from variations 1988 to 2140 found in Table 11.

TABLE 11

Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in compositions and used in methods provided herein.	
(IU rFVIII:C) to (IU rVWF:RCo)	
4:1	Var. 1988
3:1	Var. 1989
2:1	Var. 1990
3:2	Var. 1991
4:3	Var. 1992
1:1	Var. 1993
5:6	Var. 1994
4:5	Var. 1995
3:4	Var. 1996
2:3	Var. 1997
3:5	Var. 1998
1:2	Var. 1999
2:5	Var. 2000
1:3	Var. 2001
1:4	Var. 2002

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TABLE 11-continued

Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in compositions and used in methods provided herein.	
(IU rFVIII:C) to (IU rVWF:RCo)	
1:5	Var. 2003
1:6	Var. 2004
4:1-1:6	Var. 2005
4:1-1:5	Var. 2006
4:1-1:4	Var. 2007
4:1-1:3	Var. 2008
4:1-2:5	Var. 2009
4:1-1:2	Var. 2010
4:1-3:5	Var. 2011
4:1-2:3	Var. 2012
4:1-3:4	Var. 2013
4:1-4:5	Var. 2014
4:1-5:6	Var. 2015
4:1-1:1	Var. 2016
4:1-4:3	Var. 2017
4:1-3:2	Var. 2018
4:1-2:1	Var. 2019
4:1-3:1	Var. 2020
3:1-1:6	Var. 2021
3:1-1:5	Var. 2022
3:1-1:4	Var. 2023
3:1-1:3	Var. 2024
3:1-2:5	Var. 2025
3:1-1:2	Var. 2026
3:1-3:5	Var. 2027
3:1-2:3	Var. 2028
3:1-3:4	Var. 2029
3:1-4:5	Var. 2030
3:1-5:6	Var. 2031
3:1-1:1	Var. 2032
3:1-4:3	Var. 2033
3:1-3:2	Var. 2034
3:1-2:1	Var. 2035
2:1-1:6	Var. 2036
2:1-1:5	Var. 2037
2:1-1:4	Var. 2038

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TABLE 11-continued

Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in compositions and used in methods provided herein.		
(IU rFVIII:C) to (IU rVWF:RCo)		
2:1-1:3	Var.	5
	2039	
2:1-2:5	Var.	
	2040	10
2:1-1:2	Var.	
	2041	
2:1-3:5	Var.	15
	2042	
2:1-2:3	Var.	
	2043	20
2:1-3:4	Var.	
	2044	
2:1-4:5	Var.	25
	2045	
2:1-5:6	Var.	
	2046	30
2:1-1:1	Var.	
	2047	
2:1-4:3	Var.	35
	2048	
2:1-3:2	Var.	
	2049	40
3:2-1:6	Var.	
	2050	
3:2-1:5	Var.	45
	2051	
3:2-1:4	Var.	
	2052	50
3:2-1:3	Var.	
	2053	
3:2-2:5	Var.	55
	2054	
3:2-1:2	Var.	
	2055	60
3:2-3:5	Var.	
	2056	
3:2-2:3	Var.	65
	2057	
3:2-3:4	Var.	
	2058	70
3:2-4:5	Var.	
	2059	
3:2-5:6	Var.	75
	2060	
3:2-1:1	Var.	
	2061	80
3:2-4:3	Var.	
	2062	
4:3-1:6	Var.	85
	2063	
4:3-1:5	Var.	
	2064	90
4:3-1:4	Var.	
	2065	
4:3-1:3	Var.	95
	2066	
4:3-2:5	Var.	
	2067	100
4:3-1:2	Var.	
	2068	
4:3-3:5	Var.	105
	2069	
4:3-2:3	Var.	
	2070	110
4:3-3:4	Var.	
	2071	
4:3-4:5	Var.	115
	2072	
4:3-5:6	Var.	
	2073	120
4:3-1:1	Var.	
	2074	

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TABLE 11-continued

Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in compositions and used in methods provided herein.		
(IU rFVIII:C) to (IU rVWF:RCo)		
1:1-1:6	Var.	2075
	2076	
1:1-1:5	Var.	
	2077	2078
1:1-1:4	Var.	
	2079	
1:1-1:3	Var.	2080
	2081	
1:1-2:5	Var.	
	2082	2083
1:1-1:2	Var.	
	2084	
1:1-3:5	Var.	2085
	2086	
1:1-2:3	Var.	
	2087	2088
1:1-3:4	Var.	
	2089	
1:1-4:5	Var.	2090
	2091	
1:1-5:6	Var.	
	2092	2093
5:6-1:6	Var.	
	2094	
5:6-1:5	Var.	2095
	2096	
5:6-1:4	Var.	
	2097	2098
5:6-1:3	Var.	
	2099	
5:6-2:5	Var.	2100
	2101	
5:6-1:2	Var.	
	2102	2103
5:6-3:5	Var.	
	2104	
5:6-2:3	Var.	2105
	2106	
5:6-3:4	Var.	
	2107	2108
5:6-4:5	Var.	
	2109	
4:5-1:6	Var.	2110
	2111	
4:5-1:5	Var.	
	2112	2113
4:5-1:4	Var.	
	2114	
4:5-1:3	Var.	2115
	2116	
4:5-2:5	Var.	
	2117	2118
4:5-1:2	Var.	
	2119	
4:5-3:5	Var.	2120
	2121	
4:5-2:3	Var.	
	2122	2123
4:5-3:4	Var.	
	2124	
3:4-1:6	Var.	2125
	2126	
3:4-1:5	Var.	
	2127	2128
3:4-1:4	Var.	
	2129	
3:4-1:3	Var.	2130
	2131	
3:4-2:5	Var.	
	2132	2133
3:4-1:2	Var.	
	2134	
	2135	

TABLE 11-continued

Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCO) in compositions and used in methods provided herein.	
(IU rFVIII:C) to (IU rVWF:RCO)	
3:4-3:5	Var.
	2111
3:4-2:3	Var.
	2112
2:3-1:6	Var.
	2113
2:3-1:5	Var.
	2114
2:3-1:4	Var.
	2115
2:3-1:3	Var.
	2116
2:3-2:5	Var.
	2117
2:3-1:2	Var.
	2118
2:3-3:5	Var.
	2119
3:5-1:6	Var.
	2120
3:5-1:5	Var.
	2121
3:5-1:4	Var.
	2122
3:5-1:3	Var.
	2123
3:5-2:5	Var.
	2124
3:5-1:2	Var.
	2125
1:2-1:6	Var.
	2126
1:2-1:5	Var.
	2127
1:2-1:4	Var.
	2128
1:2-1:3	Var.
	2129
1:2-2:5	Var.
	2130
2:5-1:6	Var.
	2131
2:5-1:5	Var.
	2132
2:5-1:4	Var.
	2133
2:5-1:3	Var.
	2134
1:3-1:6	Var.
	2135
1:3-1:5	Var.
	2136
1:3-1:4	Var.
	2137
1:4-1:6	Var.
	2138
1:4-1:5	Var.
	2139
1:5-1:6	Var.
	2140

Var. = Variation

In specific aspects, the rVWF and/or the FVIII (recombinant or plasma derived) used in accordance with the present invention are not modified with any conjugation, post-translation or covalent modifications. In particular embodiments, the rVWF and/or FVIII of the present invention are not modified with a water soluble polymer, including without limitation, a polyethylene glycol (PEG), a polypropylene glycol, a polyoxyalkylene, a polysialic acid, hydroxyl ethyl starch, a poly-carbohydrate moiety, and the like.

In other aspects, the rVWF and/or the FVIII (recombinant or plasma derived) used in accordance with the present invention are modified through conjugation, post-translation modification, or covalent modification, including modifications of the N- or C-terminal residues as well as modifications of selected side chains, for example, at free sulfhydryl-groups, primary amines, and hydroxyl-groups. In one embodiment, a water soluble polymer is linked to the protein (directly or via a linker) by a lysine group or other primary amine. In one embodiment, the rVWF and/or FVIII proteins of the present invention may be modified by conjugation of a water soluble polymer, including without limitation, a polyethylene glycol (PEG), a polypropylene glycol, a polyoxyalkylene, a polysialic acid, hydroxyl ethyl starch, a poly-carbohydrate moiety, and the like.

Water soluble polymers that may be used to modify the rVWF and/or FVIII include linear and branched structures. The conjugated polymers may be attached directly to the coagulation proteins of the invention, or alternatively may be attached through a linking moiety. Non-limiting examples of protein conjugation with water soluble polymers can be found in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192, and 4,179,337, as well as in Abuchowski and Davis "Enzymes as Drugs," Holcenberg and Roberts, Eds., pp. 367 383, John Wiley and Sons, New York (1981), and Hermanson G., Bioconjugate Techniques 2nd Ed., Academic Press, Inc. 2008.

Protein conjugation may be performed by a number of well known techniques in the art, for example, see Hermanson G., Bioconjugate Techniques 2nd Ed., Academic Press, Inc. 2008. Examples include linkage through the peptide bond between a carboxyl group on one of either the coagulation protein or water-soluble polymer moiety and an amine group of the other, or an ester linkage between a carboxyl group of one and a hydroxyl group of the other. Another linkage by which a coagulation protein of the invention could be conjugated to a water-soluble polymer compound is via a Schiff base, between a free amino group on the polymer moiety being reacted with an aldehyde group formed at the non-reducing end of the polymer by periodate oxidation (Jennings and Lugowski, J. Immunol. 1981; 127:1011-8; Fernandes and Gregonradis, Biochim Biophys Acta. 1997; 1341; 26-34). The generated SchiffBase can be stabilized by specific reduction with NaCNBH₃ to form a secondary amine. An alternative approach is the generation of terminal free amino groups on the polymer by reductive amination with NH₄Cl after prior oxidation. Bifunctional reagents can be used for linking two amino or two hydroxyl groups. For example a polymer containing an amino group can be coupled to an amino group of the coagulation protein with reagents like BS3 (Bis(sulfosuccinimidyl)suberate/Pierce, Rockford, Ill.). In addition hetero-bifunctional cross linking reagents like Sulfo-EMCS (N-ε-Maleimidocaproyloxy) sulfosuccinimide ester/Pierce) can be used for instance to link amine and thiol groups. In other embodiments, an aldehyde reactive group, such as PEG alkoxide plus diethyl acetal of bromoacetaldehyde; PEG plus DMSO and acetic anhydride, and PEG chloride plus the phenoxide of 4-hydroxybenzaldehyde, succinimidyl active esters, activated dithiocarbonate PEG, 2,4,5-trichlorophenylchloroformate and P-nitrophenylchloroformate activated PEG, may be used in the conjugation of a coagulation protein.

In some aspects, the rVWF used in methods of the present invention has been matured in vitro with Furin. In further embodiments, the Furin is recombinant Furin.

In further aspects, the rVWF and/or rFVIII used in the methods of the present invention are produced by expression in a mammalian cell culture using methods known in the art.

In particular embodiments, the mammalian culture comprises CHO cells. In further embodiments, the rVWF and the rFVIII are co-expressed in the same culture. In such embodiments, the rVWF and the rFVIII are purified together (co-purified) or separately using methods known in the art. In other embodiments, the rVWF and the rFVIII are expressed in different cultures.

In an exemplary embodiment, the rVWF of the invention comprises rVWF protein isolated from a CHO cell expression system. In a further embodiment, the propeptide removal is mediated in vitro through exposure of the pro-VWF to Furin—in a still further embodiment, the Furin used for propeptide removal is recombinant Furin. In as yet further embodiment, fully glycosylated/ABO blood group glycans are absent.

In yet further embodiments, the rVWF used in methods and compositions of the present invention by expression in a suitable eukaryotic host system. Examples of eukaryotic cells include, without limitation, mammalian cells, such as CHO, COS, HEK 293, BHK, SK-Hep, and HepG2; insect cells, e.g., SF9 cells, SF21 cells, S2 cells, and High Five cells; and yeast cells, e.g., *Saccharomyces* or *Schizosaccharomyces* cells. In one embodiment, the VWF can be expressed in yeast cells, insect cells, avian cells, mammalian cells, and the like. For example, in a human cell line, a hamster cell line, or a murine cell line. In one particular embodiment, the cell line is a CHO, BHK, or HEK cell line. Typically, mammalian cells, e.g., CHO cell from a continuous cell line, can be used to express the VWF of the present invention.

In certain embodiments, the nucleic acid sequence comprising a sequence coding for VWF can be a vector. The vector can be delivered by a virus or can be a plasmid. The nucleic acid sequence coding for the protein can be a specific gene or a biologically functional part thereof. In one embodiment, the protein is at least a biologically active part of VWF.

A wide variety of vectors can be used for the expression of the VWF and can be selected from eukaryotic expression vectors. Examples of vectors for eukaryotic expression include: (i) for expression in yeast, vectors such as pAO, pPIC, pYES, pMET, using promoters such as AOX1, GAP, GAL1, AUG1, etc.; (ii) for expression in insect cells, vectors such as pMT, pAc5, pIB, pMIB, pBAC, etc., using promoters such as PH, p10, MT, Ac5, OpIE2, gp64, polh, etc., and (iii) for expression in mammalian cells, vectors such as pSVL, pCMV, pRc/RSV, pCDNA3, pBPV, etc., and vectors derived from viral systems such as vaccinia virus, adeno-associated viruses, herpes viruses, retroviruses, etc., using promoters such as CMV, SV40, EF-1, UbC, RSV, ADV, BPV, and β -actin.

In some embodiments of the present invention, the nucleic acid sequence further comprises other sequences suitable for a controlled expression of a protein such as promoter sequences, enhancers, TATA boxes, transcription initiation sites, polylinkers, restriction sites, poly-A-sequences, protein processing sequences, selection markers, and the like which are generally known to a person of ordinary skill in the art.

In certain embodiments, the cell-culture methods of the invention may comprise the use of a microcarrier. In some embodiments, the cell-cultures of the embodiments can be performed in large bioreactors under conditions suitable for providing high volume-specific culture surface areas to achieve high cell densities and protein expression. One means for providing such growth conditions is to use microcarriers for cell-culture in stirred tank bioreactors. The concept of cell-growth on microcarriers was first described by van Wezel (van Wezel, A. L., *Nature* 216:64-5 (1967)) and allows for cell attachment on the surface of small solid particles suspended

in the growth medium. These methods provide for high surface-to-volume ratios and thus allow for efficient nutrient utilization. Furthermore, for expression of secreted proteins in eukaryotic cell lines, the increased surface-to-volume ratio allows for higher levels of secretion and thus higher protein yields in the supernatant of the culture. Finally, these methods allow for the easy scale-up of eukaryotic expression cultures.

The cells expressing VWF can be bound to a spherical or a porous microcarrier during cell culture growth. The microcarrier can be a microcarrier selected from the group of microcarriers based on dextran, collagen, plastic, gelatine and cellulose and others as described in Butler (1988. In: Spier & Griffiths, *Animal Cell Biotechnology* 3:283-303). It is also possible to grow the cells to a biomass on spherical microcarriers and subculture the cells when they have reached final fermenter biomass and prior to production of the expressed protein on a porous microcarrier or vice versa. Suitable spherical microcarriers can include smooth surface microcarriers, such as Cytodex™ 1, Cytodex™ 2, and Cytodex™ 3 (GE Healthcare) and macroporous microcarriers such as Cytopore™ 1, Cytopore™ 2, Cytoline™ 1, and Cytoline™ 2 (GE Healthcare).

In certain embodiments, rVWF is expressed in cells cultured in cell culture media that produces high molecular weight rVWF. The terms “cell culture solution,” “cell culture medium or media,” and “cell culture supernatant” refer to aspects of cell culture processes generally well known in the art. In the context of the present invention, a cell culture solution can include cell culture media and cell culture supernatant. The cell culture media are externally added to the cell culture solution, optionally together with supplements, to provide nutrients and other components for culturing the cells expressing VWF. The cell culture supernatant refers to a cell culture solution comprising the nutrients and other components from the cell culture medium as well as products released, metabolized, and/or excreted from the cells during culture. In further embodiments, the media can be animal protein-free and chemically defined. Methods of preparing animal protein-free and chemically defined culture media are known in the art, for example in US 2008/0009040 and US 2007/0212770, which are both incorporated herein for all purposes and in particular for all teachings related to cell culture media. “Protein free” and related terms refers to protein that is from a source exogenous to or other than the cells in the culture, which naturally shed proteins during growth. In another embodiment, the culture medium is polypeptide free. In another embodiment, the culture medium is serum free. In another embodiment the culture medium is animal protein free. In another embodiment the culture medium is animal component free. In another embodiment, the culture medium contains protein, e.g., animal protein from serum such as fetal calf serum. In another embodiment, the culture has recombinant proteins exogenously added. In another embodiment, the proteins are from a certified pathogen free animal. The term “chemically defined” as used herein shall mean, that the medium does not comprise any undefined supplements, such as, for example, extracts of animal components, organs, glands, plants, or yeast. Accordingly, each component of a chemically defined medium is accurately defined. In a preferred embodiment, the media are animal-component free and protein free.

In certain embodiments, the culture of cells expressing VWF can be maintained for at least about 7 days, or at least about 14 days, 21 days, 28 days, or at least about 5 weeks, 6 weeks, 7 weeks, or at least about 2 months, or 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 months or longer. The cell density at which a cell-culture is maintained at for production

of a recombinant VWF protein will depend upon the culture-conditions and medium used for protein expression. One of skill in the art will readily be able to determine the optimal cell density for a cell-culture producing an VWF. In one embodiment, the culture is maintained at a cell density of between about 0.5×10^6 and 4×10^7 cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about 1.0×10^6 and about 1.0×10^7 cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about 1.0×10^6 and about 4.0×10^6 cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about 1.0×10^6 and about 4.0×10^6 cells/ml for an extended period of time. In yet other embodiments, the cell density may be maintained at a concentration between about 2.0×10^6 and about 4.0×10^6 , or between about 1.0×10^6 and about 2.5×10^6 , or between about 1.5×10^6 and about 3.5×10^6 , or any other similar range, for an extended period of time. After an appropriate time in cell culture, the rVWF can be isolated from the expression system using methods known in the art.

In a specific embodiment, the cell density of the continuous cell culture for production of rVWF is maintained at a concentration of no more than 2.5×10^6 cells/mL for an extended period. In other specific embodiments, the cell density is maintained at no more than 2.0×10^6 cells/mL, 1.5×10^6 cells/mL, 1.0×10^6 cells/mL, 0.5×10^6 cells/mL, or less. In one embodiment, the cell density is maintained at between 1.5×10^6 cells/mL and 2.5×10^6 cells/mL.

In one specific embodiment of the cell cultures described above, the cell culture solution comprises a medium supplement comprising copper. Such cell culture solutions are described for example in US 2012/0035110, filed Jul. 8, 2011, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to cell culture methods and compositions for producing recombinant VWF.

In further embodiments, subsequent to purification (separately or together) from a mammalian cell culture, the rFVIII/rVWF complex is reconstituted prior to administration. In still further embodiments, the rVWF is treated with Furin prior to or subsequent to reconstitution of the rFVIII/rVWF complex. In further embodiments, the Furin is recombinant Furin.

In still further embodiments, the rVWF of the invention is not exposed to ADAMTS13, with the result that ultra large (i.e., comprising 10 or more subunits) are present in rVWF compositions of the invention.

In specific aspects, the rVWF and/or the rFVIII used in methods of the present invention are contained in a formulation containing a buffer, a sugar and/or a sugar alcohol (including without limitation trehalose and mannitol), a stabilizer (such as glycine), and a surfactant (such as Polysorbate 80). In further embodiments, for formulations containing rFVIII, the formulation may further include sodium, histidine, calcium, and glutathione.

In one aspect, the formulations comprising rVWF and/or rFVIII are lyophilized prior to administration. Lyophilization is carried out using techniques common in the art and should be optimized for the composition being developed [Tang et al., Pharm Res. 21:191-200. (2004) and Chang et al., Pharm Res. 13:243-9 (1996)].

Methods of preparing pharmaceutical formulations can include one or more of the following steps: adding a stabilizing agent as described herein to said mixture prior to lyophilizing, adding at least one agent selected from a bulking agent, an osmolality regulating agent, and a surfactant, each

of which as described herein, to said mixture prior to lyophilization. A lyophilized formulation is, in one aspect, at least comprised of one or more of a buffer, a bulking agent, and a stabilizer. In this aspect, the utility of a surfactant is evaluated and selected in cases where aggregation during the lyophilization step or during reconstitution becomes an issue. An appropriate buffering agent is included to maintain the formulation within stable zones of pH during lyophilization.

The standard reconstitution practice for lyophilized material is to add back a volume of pure water or sterile water for injection (WFI) (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration [Chen, Drug Development and Industrial Pharmacy, 18:1311-1354 (1992)]. Accordingly, methods are provided for preparation of reconstituted recombinant VWF (with or without recombinant Factor VIII) compositions comprising the step of adding a diluent to a lyophilized recombinant VWF composition of the invention.

The lyophilized material may be reconstituted as an aqueous solution. A variety of aqueous carriers, e.g., sterile water for injection, water with preservatives for multi dose use, or water with appropriate amounts of surfactants (for example, an aqueous suspension that contains the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions). In various aspects, such excipients are suspending agents, for example and without limitation, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum *acacia*; dispersing or wetting agents are a naturally-occurring phosphatide, for example and without limitation, lecithin, or condensation products of an alkylene oxide with fatty acids, for example and without limitation, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example and without limitation, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example and without limitation, polyethylene sorbitan monooleate. In various aspects, the aqueous suspensions also contain one or more preservatives, for example and without limitation, ethyl, or n-propyl, p-hydroxybenzoate.

In certain embodiments, compositions of the present invention are liquid formulations for administration with the use of a syringe or other storage vessel. In further embodiments, these liquid formulations are produced from lyophilized material described herein reconstituted as an aqueous solution.

In a further aspect, the compositions of the invention further comprise one or more pharmaceutically acceptable carriers. The phrases "pharmaceutically" or "pharmacologically" acceptable refer to molecular entities and compositions that are stable, inhibit protein degradation such as aggregation and cleavage products, and in addition do not produce allergic, or other adverse reactions when administered using routes well-known in the art, as described below. "Pharmaceutically acceptable carriers" include any and all clinically useful solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like, including those agents disclosed above.

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Administration of Compositions of the Invention for Methods of Treating Disease

One of the advantages of administering rVWF to subjects to treat coagulation disease is that the higher specific activity of rVWF as compared to pdVWF allows flexibility in the amount of rVWF administered and the number of times the subject is re-dosed with rVWF (with or without co-administered FVIII). In addition, rVWF compositions provide the further flexibility of re-dosing with rVWF alone after an initial co-administration of rVWF and FVIII, without need for additional dosing with FVIII. As will be appreciated and as is discussed in further detail herein, the co-administered FVIII may be recombinant or plasma derived.

In one aspect, the administration of rVWF in accordance with the invention results in higher plasma FVIII levels and/or activity in the subject than is seen with a subject administered pdVWF. As discussed above, increases in FVIII levels and activity can be measured using methods standard in the art, thus allowing for determination of appropriate dosages for rVWF with or without FVIII.

Single or multiple administrations of rVWF (with or without FVIII) are carried out with the dose levels and pattern being selected by the treating physician. For the prevention or treatment of disease, the appropriate dosage depends on the type of disease to be treated (e.g., von Willebrand disease), the severity and course of the disease, whether drug is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the drug, and the discretion of the attending physician.

In further embodiments and in accordance with any of the above, treatment of coagulation diseases such as VWD or Hemophilia A may involve an initial treatment of rVWF alone or in combination with FVIII, followed by one or more repeat doses of rVWF alone, rVWF plus FVIII together, or FVIII alone. The nature of the initial and then the subsequent repeat administrations will depend in part on the disease being treated. For example, patients with VWD have some level of FVIII, but the stability of that FVIII is generally compromised because these patients lack VWF. Treatment of VWD patients may thus in some embodiments involve an initial treatment with both rVWF and rFVIII followed by repeated administrations of rVWF alone. In other embodiments, the initial treatment may be with rVWF alone while subsequent repeated administrations are with both rVWF and rFVIII. In still other embodiments, the initial and subsequent repeat administrations may all include a co-administration of both rVWF and rFVIII. Similarly, Hemophilia A patients (who lack FVIII) may receive an initial treatment of both rVWF and rFVIII, and subsequent repeat treatments may comprise the administration of rFVIII alone or rVWF alone. In other embodiments, the initial treatment may be rFVIII alone while the subsequent repeat treatments involve co-administration of rVWF and rFVIII.

In further aspects, rVWF is administered to a subject in doses ranging from 0.5 IU/kg-200 IU/kg. In some embodiments, rVWF is administered in doses ranging from 1-190, 5-180, 10-170, 15-160, 20-150, 25-140, 30-130, 35-120, 40-110, 45-100, 50-90, 55-80, or 60-70 IU/kg. In further embodiments and in accordance with any of the above, rVWF (with or without FVIII) is administered to a subject at doses of between about 1 IU/kg to about 150 IU/kg rVWF. In still further embodiments, the rVWF and rFVIII is administered at doses of between 1.5 IU/kg to 150 IU/kg, 2 IU/kg to 50 IU/kg, 5 IU/kg to 40 IU/kg, 10 IU/kg to 20 IU/kg, 10 IU/kg to 100 IU/kg, 25 IU/kg to 75 IU/kg, and 40 IU/kg to 75 IU/kg. In still further embodiments, rVWF is administered at 2, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 IU/kg. As will be appreciated

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and as is discussed further herein, appropriate dosages of rVWF (or rVWF together with FVIII) may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data.

In one embodiment, rVWF is administered to a subject in a dose selected from variations 2141 to 2338 in Table 12.

TABLE 12

Exemplary embodiments for the dosage of rVWF administered to a subject according to the methods provided herein.

IU/kg	
About 0.5	Var. 2141
About 1	Var. 2142
About 2	Var. 2143
About 3	Var. 2144
About 4	Var. 2145
About 5	Var. 2146
About 10	Var. 2147
About 15	Var. 2148
About 20	Var. 2149
About 25	Var. 2150
About 30	Var. 2151
About 35	Var. 2152
About 40	Var. 2153
About 45	Var. 2154
About 50	Var. 2155
About 55	Var. 2156
About 60	Var. 2157
About 65	Var. 2158
About 70	Var. 2159
About 75	Var. 2160
About 80	Var. 2161
About 85	Var. 2162
About 90	Var. 2163
About 95	Var. 2164
About 100	Var. 2165
About 105	Var. 2166
About 110	Var. 2167
About 115	Var. 2168
About 120	Var. 2169
About 125	Var. 2170
About 130	Var. 2171
About 135	Var. 2172
About 140	Var. 2173
About 145	Var. 2174
About 150	Var. 2175
About 155	Var. 2176
About 160	Var. 2177
About 165	Var. 2178
About 170	Var. 2179
About 175	Var. 2180
About 180	Var. 2181
About 185	Var. 2182
About 190	Var. 2183
About 195	Var. 2184
About 200	Var. 2185
0.5-200	Var. 2186
0.5-175	Var. 2187
0.5-150	Var. 2188
0.5-125	Var. 2189
0.5-100	Var. 2190
0.5-75	Var. 2191
0.5-50	Var. 2192
0.5-40	Var. 2193
0.5-30	Var. 2194
0.5-25	Var. 2195
0.5-20	Var. 2196
0.5-15	Var. 2197
0.5-10	Var. 2198
0.5-7.5	Var. 2199
0.5-5	Var. 2200
0.5-2.5	Var. 2201
0.5-1	Var. 2202
1-200	Var. 2203
1-175	Var. 2204
1-150	Var. 2205
1-125	Var. 2206

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TABLE 12-continued

Exemplary embodiments for the dosage of rVWF administered to a subject according to the methods provided herein.	
IU/kg	
1-100	Var. 2207
1-75	Var. 2208
1-50	Var. 2209
1-40	Var. 2210
1-30	Var. 2211
1-25	Var. 2212
1-20	Var. 2213
1-15	Var. 2214
1-10	Var. 2215
1-7.5	Var. 2216
1-5	Var. 2217
1-2.5	Var. 2218
2.5-200	Var. 2219
2.5-175	Var. 2220
2.5-150	Var. 2221
2.5-125	Var. 2222
2.5-100	Var. 2223
2.5-75	Var. 2224
2.5-50	Var. 2225
2.5-40	Var. 2226
2.5-30	Var. 2227
2.5-25	Var. 2228
2.5-20	Var. 2229
2.5-15	Var. 2230
2.5-10	Var. 2231
2.5-7.5	Var. 2232
2.5-5	Var. 2233
5-200	Var. 2234
5-175	Var. 2235
5-150	Var. 2236
5-125	Var. 2237
5-100	Var. 2238
5-75	Var. 2239
5-50	Var. 2240
5-40	Var. 2241
5-30	Var. 2242
5-25	Var. 2243
5-20	Var. 2244
5-15	Var. 2245
5-10	Var. 2246
5-7.5	Var. 2247
7.5-200	Var. 2248
7.5-175	Var. 2249
7.5-150	Var. 2250
7.5-125	Var. 2251
7.5-100	Var. 2252
7.5-75	Var. 2253
7.5-50	Var. 2254
7.5-40	Var. 2255
7.5-30	Var. 2256
7.5-25	Var. 2257
7.5-20	Var. 2258
7.5-15	Var. 2259
7.5-10	Var. 2260
10-200	Var. 2261
10-175	Var. 2262
10-150	Var. 2263
10-125	Var. 2264
10-100	Var. 2265
10-75	Var. 2266
10-50	Var. 2267
10-40	Var. 2268
10-30	Var. 2269
10-25	Var. 2270
10-20	Var. 2271
10-15	Var. 2272
15-200	Var. 2273
15-175	Var. 2274
15-150	Var. 2275
15-125	Var. 2276
15-100	Var. 2277
15-75	Var. 2278
15-50	Var. 2279
15-40	Var. 2280
15-30	Var. 2281

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TABLE 12-continued

Exemplary embodiments for the dosage of rVWF administered to a subject according to the methods provided herein.	
IU/kg	
15-25	Var. 2282
15-20	Var. 2283
20-200	Var. 2284
20-175	Var. 2285
20-150	Var. 2286
20-125	Var. 2287
20-100	Var. 2288
20-75	Var. 2289
20-50	Var. 2290
20-40	Var. 2291
20-30	Var. 2292
20-25	Var. 2293
25-200	Var. 2294
25-175	Var. 2295
25-150	Var. 2296
25-125	Var. 2297
25-100	Var. 2298
25-75	Var. 2299
25-50	Var. 2300
25-40	Var. 2301
25-30	Var. 2302
30-200	Var. 2303
30-175	Var. 2304
30-150	Var. 2305
30-125	Var. 2306
30-100	Var. 2307
30-75	Var. 2308
30-50	Var. 2309
30-40	Var. 2310
40-200	Var. 2311
40-175	Var. 2312
40-150	Var. 2313
40-125	Var. 2314
40-100	Var. 2315
40-75	Var. 2316
40-50	Var. 2317
50-200	Var. 2318
50-175	Var. 2319
50-150	Var. 2320
50-125	Var. 2321
50-100	Var. 2322
50-75	Var. 2323
75-200	Var. 2324
75-175	Var. 2325
75-150	Var. 2326
75-125	Var. 2327
75-100	Var. 2328
100-200	Var. 2329
100-175	Var. 2330
100-150	Var. 2331
100-125	Var. 2332
125-200	Var. 2333
125-175	Var. 2334
125-150	Var. 2335
150-200	Var. 2336
150-200	Var. 2337
175-200	Var. 2338

Var. = Variation

55 In still further embodiments, rVWF is administered at a dose such that it increases half-life of plasma FVIII by about 1.0-4.5, 1.5-4.0, 2.0-3.5, 2.5-3.0 fold. In still further embodiments, the dose and/or frequency of rVWF administration is such that the increase in FVIII half-life is maintained at least

60 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the dose and/or frequency of rVWF administration is such that the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration

65 of rVWF. In one embodiment, rVWF is administered at a dose such that it increases the half-life of plasma FVIII by a value selected from variations 1046 to 1089 found in Table 7.

As discussed above, the rVWF of the invention shows an increased effect on the stability of FVIII as compared to the effect of pdVWF. In certain aspects, rVWF is administered at a dose and/or with a frequency such that it increases average FVIII half-life by about 1-15, 2-14, 3-13, 4-12, 5-11, 6-10, 5-9, 6-8 hours. In still further embodiments, rVWF is administered at a dose and/or frequency such that it increases FVIII half-life by about 10% to about 75% as compared to pdVWF. In yet further embodiments, rVWF increases FVIII half-life by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. As will be appreciated, the increase in FVIII stability, half-life and/or activity can be assessed using methods known in the art, including without limitation coagulation assays. In other embodiments, administration of rVWF increases the half-life of FVIII by an amount selected from variations 1300 to 1643 found in Table 9, as compared to administration of plasma-derived VWF.

As discussed herein, the stabilization of FVIII activity by rVWF as compared to pdVWF can be measured by metrics in addition to FVIII half-life, including mean residence time (MRT) and area under curve (AUC). In exemplary embodiments, rVWF is administered at a dose and/or frequency such that it increases MRT by about 1-15 hours as compared to pdVWF. In further embodiments, rVWF increases MRT by about 1-25, 2-20, 3-15, 4-10, 5-9, 6-8 hours as compared to pdVWF. In still further embodiments, rVWF increases FVIII MRT by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in MRT is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. In other embodiments, administration of rVWF increases the MRT of FVIII by an amount selected from variations 1300 to 1643 found in Table 9, as compared to administration of plasma-derived VWF.

In further aspects, the doses of rVWF administered to patients are comparable to doses used in administration of pdVWF/pdFVIII.

Compositions of rVWF with or without FVIII can be contained in pharmaceutical formulations, as described herein. Such formulations can be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Generally, compositions are essentially free of pyrogens, as well as other impurities that could be harmful to the recipient.

In one aspect, formulations of the invention are administered by an initial bolus followed by a continuous infusion to maintain therapeutic circulating levels of drug product. As another example, the inventive compound is administered as a one-time dose. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The route of administration can

be, but is not limited to, by intravenous, intraperitoneal, subcutaneous, or intramuscular administration. The frequency of dosing depends on the pharmacokinetic parameters of the agents and the route of administration. The optimal pharmaceutical formulation is determined by one skilled in the art depending upon the route of administration and desired dosage. See for example, Remington's Pharmaceutical Sciences, 18th Ed., 1990, Mack Publishing Co., Easton, Pa. 18042 pages 1435-1712, the disclosure of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to formulations, routes of administration and dosages for pharmaceutical products. Such formulations influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the administered agents. Depending on the route of administration, a suitable dose is calculated according to body weight, body surface area or organ size. Appropriate dosages may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. The final dosage regimen is determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. By way of example, a typical dose of a recombinant VWF of the present invention is approximately 50 U/kg, equal to 500 µg/kg. As studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

In some embodiments, rVWF is administered to a subject alone. In some embodiments, rVWF is administered to a subject in combination with one or more coagulation factors. In further embodiments, the coagulation factor administered with rVWF is FVIII. In still further embodiments rVWF is administered prior to, subsequent to, or simultaneously with a coagulation factor such as FVIII. In certain embodiments, rVWF and FVIII are administered together in a single composition. As will be appreciated, the FVIII that is co-administered with rVWF can be either recombinant FVIII or plasma derived.

In further embodiments, rVWF (with or without FVIII) is administered to a subject no more than once daily. In further embodiments, rVWF (with or without FVIII) is administered to a subject: no more than once every other day, no more than once every third day, no more than once every fourth day, no more than once every fifth day, no more than once a week, no more than once every two weeks, no more than once a month. In still further embodiments, rVWF (with or without FVIII) is administered to a subject no more than twice a day.

In further embodiments, rVWF and FVIII are administered together to a subject in an initial dose, and then subsequent re-dosing is conducted with rVWF alone. In other embodiments, re-dosing is conducted with both rVWF and FVIII.

In still further embodiments, rVWF (with or without rFVIII) is administered at a dose such that plasma FVIII activity is stabilized for about 10 to about 90 hours. In further embodiments, plasma FVIII activity is stabilized for at least 12, 24, 36, 48 or 72 hours. As will be appreciated, the stabilized plasma FVIII activity may be that of endogenous FVIII, co-administered FVIII (plasma-derived or recombinant) or a combination of both endogenous and co-administered FVIII.

In some embodiments, rVWF and FVIII are administered together at a dose such that extension of in vivo half-life of plasma FVIII activity is stabilized for at least 12, 24, 36, 48 or 72 hours. In further embodiments, the plasma FVIII activity is

stabilized for about 10 to about 90 hours. In still further embodiments, the increase in half-life of plasma FVIII is maintained for at least 24, 36, 48, 72, 90, 120, or 168 hours in a patient. The co-administered FVIII can be rFVIII or pdFVIII. In some embodiments, plasma FVIII activity is stabilized for a time selected from variations 1090 to 1299 found in Table 8, after co-administration of rVWF and FVIII.

In preferred aspects, the present invention provides methods for treating coagulation disease, including hemophilia and von Willebrand Disease (VWD).

As used herein, the terms “hemophilia” or “haemophilia” refer to a group of disease states broadly characterized by reduced blood clotting or coagulation. Hemophilia may refer to Type A, Type B, or Type C hemophilia, or to the composite of all three diseases types. Type A hemophilia (hemophilia A) is caused by a reduction or loss of factor VIII (FVIII) activity and is the most prominent of the hemophilia subtypes. Type B hemophilia (hemophilia B) results from the loss or reduction of factor IX (FIX) clotting function. Type C hemophilia (hemophilia C) is a consequence of the loss or reduction in factor XI (FXI) clotting activity. Hemophilia A and B are X-linked diseases, while hemophilia C is autosomal. Common treatments for hemophilia include both prophylactic and on-demand administration of clotting factors, such as FVIII, FIX, including Bebulin®-VH, and FXI, as well as FEIBA-VH, desmopressin, and plasma infusions.

As used herein “von Willebrand Disease” refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump together and stick to the blood vessel wall, which is necessary for normal blood clotting. There are several types of Von Willebrand disease. The following table summarizes the characteristics of different types of VWD:

Type	Characteristics
Type 1	Quantitative forms of VWD Partial quantitative deficiencies of VWF VWF plasma levels that are 5% to 30% of normal approximately 60% to 80% of patients
Type 3	Virtually complete deficiency of VWF Approximately 1% to 5% of patients
Type 2	Qualitative forms of VWD Approximately 10% to 30% of patients
Type 2A	Decreased VWF-dependent platelet adhesion Selective deficiency of HMW-VWF multimers Platelet binding functions of VWF are impaired
Type 2B	Gain of function mutation with increased VWF binding to platelets Loss of HMW-VWF multimers from plasma, but not from platelets Loss of both VWF and platelets through a clearance mechanism
Type 2M	Decreased VWF-dependent platelet adhesion without selective deficiency of HMW-VWF multimers
Type 2N	Markedly decreased binding affinity for factor VIII

Adopted from Sadler, *J Thromb Haemost* 2006; 4, 2103

Methods for treating coagulation disease include administering rVWF or a combination of rVWF rFVIII to subjects in need thereof in accordance with any of the methods of administration described herein and known in the art. Such subjects may be suffering from any coagulation disease, including without limitation von Willebrand Disease or hemophilia. As will be appreciated, any type of von Willebrand Disease, including any of the types listed in the above table, can be treated in accordance with any of the methods and compositions described herein.

In some embodiments, rVWF (with or without rFVIII) is administered to a subject such that the level of Factor VIII

procoagulant activity (FVIII:C) in the plasma of the subject 24, 36, 48 or more hours post-administration is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration. In further embodiments, the level of the FVIII:C in the plasma of the subject 24, 36, 48 or more hours post-administration is at least between 50% and 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration. In still further embodiments, the level of the FVIII:C in the plasma of the subject 24, 36, 48 or more hours post-administration is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

Administration of rVWF

In one aspect, the present disclosure provides method for treating Von Willebrand Disease (VWD) or Hemophilia A in a subject in need thereof, which includes administering a composition of recombinant Von Willebrand Factor (rVWF) such that Factor VIII (FVIII) stability is increased, as compared to FVIII half-life in a subject administered a composition of plasma derived Von Willebrand Factor (pdVWF). In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 10%, 20%, 30%, 2 hr, 4 hr, 6 hr, or by an amount selected from variations 1300 to 1643 found in Table 9, as compared to FVIII stability in a subject administered a composition of pdVWF. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 10% as compared to FVIII stability in a subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII sta-

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bility is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 20% as compared to FVIII stability in a subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 30% as compared to FVIII stability in a subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high

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molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

TABLE 13

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.									
Increased Stability (Hours)									
	at least 1 hr	at least 2 hr	at least 3 hr	at least 4 hr	at least 5 hr	at least 6 hr	at least 7 hr	at least 8 hr	
(mU/ μ g)	at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
20	2339	2385	2431	2477	2523	2569	2615	2661	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
30	2340	2386	2432	2478	2524	2570	2616	2662	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
40	2341	2387	2433	2479	2525	2571	2617	2663	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
50	2342	2388	2434	2480	2526	2572	2618	2664	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
60	2343	2389	2435	2481	2527	2573	2619	2665	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
70	2344	2390	2436	2482	2528	2574	2620	2666	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
80	2345	2391	2437	2483	2529	2575	2621	2667	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
90	2346	2392	2438	2484	2530	2576	2622	2668	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
100	2347	2393	2439	2485	2531	2577	2623	2669	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
125	2348	2394	2440	2486	2532	2578	2624	2670	
at least	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
150	2349	2395	2441	2487	2533	2579	2625	2671	
20-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2350	2396	2442	2488	2534	2580	2626	2672	
20-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2351	2397	2443	2489	2535	2581	2627	2673	
20-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2352	2398	2444	2490	2536	2582	2628	2674	
20-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2353	2399	2445	2491	2537	2583	2629	2675	
20-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2354	2400	2446	2492	2538	2584	2630	2676	
20-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2355	2401	2447	2493	2539	2585	2631	2677	
20-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2356	2402	2448	2494	2540	2586	2632	2678	
20-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
	2357	2403	2449	2495	2541	2587	2633	2679	

TABLE 13-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	at least 1 hr	at least 2 hr	at least 3 hr	at least 4 hr	at least 5 hr	at least 6 hr	at least 7 hr	at least 8 hr
20-40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2358	2404	2450	2496	2542	2588	2634	2680
40-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2359	2405	2451	2497	2543	2589	2635	2681
40-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2360	2406	2452	2498	2544	2590	2636	2682
40-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2361	2407	2453	2499	2545	2591	2637	2683
40-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2362	2408	2454	2500	2546	2592	2638	2684
40-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2363	2409	2455	2501	2547	2593	2639	2685
40-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2364	2410	2456	2502	2548	2594	2640	2686
40-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2365	2411	2457	2503	2549	2595	2641	2687
40-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2366	2412	2458	2504	2550	2596	2642	2688
60-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2367	2413	2459	2505	2551	2597	2643	2689
60-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2368	2414	2460	2506	2552	2598	2644	2690
60-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2369	2415	2461	2507	2553	2599	2645	2691
60-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2370	2416	2462	2508	2554	2600	2646	2692
60-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2371	2417	2463	2509	2555	2601	2647	2693
60-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2372	2418	2464	2510	2556	2602	2648	2694
70-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2373	2419	2465	2511	2557	2603	2649	2695
70-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2374	2420	2466	2512	2558	2604	2651	2696
70-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2375	2421	2467	2513	2559	2605	2651	2697
70-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2376	2422	2468	2514	2560	2606	2652	2698
70-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2377	2423	2469	2515	2561	2607	2653	2699
80-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2378	2424	2470	2516	2562	2608	2654	2700
80-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2379	2425	2471	2517	2563	2609	2655	2701
80-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2380	2426	2472	2518	2564	2610	2656	2702
80-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2381	2427	2473	2519	2565	2611	2657	2703
90-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2382	2428	2474	2520	2566	2612	2658	2704
90-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2383	2429	2475	2521	2567	2613	2659	2705
90-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2384	2430	2476	2522	2568	2614	2660	2706

Var. = Variation

TABLE 14

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.									
Increased Stability (Hours)									
	1-8 hr	1-7 hr	1-6 hr	1-5 hr	1-4 hr	1-3 hr	1-2 hr	2-8 hr	
(mU/ μ g)	at least 20	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
		2707	2753	2799	2845	2891	2937	2983	3029
	at least 30	Var.	Var.	Var.	Var.	Var.	Var.	Var.	
		2708	2754	2800	2846	2892	2938	2984	3030

TABLE 14-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	1-8 hr	1-7 hr	1-6 hr	1-5 hr	1-4 hr	1-3 hr	1-2 hr	2-8 hr
at least 40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2709	2755	2801	2847	7893	2939	2985	3031
at least 50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2710	2756	2802	2848	2894	2940	2986	3032
at least 60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2711	2757	2803	2849	2895	2941	2987	3033
at least 70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2712	2758	2804	2850	2896	2942	2988	3034
at least 80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2713	2759	2805	2851	2897	2943	2989	3035
at least 90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2714	2760	2806	2852	2898	2944	2990	3036
at least 100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2715	2761	2807	2853	2899	2945	2991	3037
at least 125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2716	2762	2808	2854	2900	2946	2992	3038
at least 150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2717	2763	2809	2855	2901	2947	2993	3039
20-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2718	2764	2810	2856	2902	2948	2994	3040
20-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2719	2765	2811	2857	2903	2949	2995	3041
20-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2720	2766	2812	2858	2904	2950	2996	3042
20-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2721	2767	2813	2859	2905	2951	2997	3043
20-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2722	2768	2814	2860	2906	2952	2998	3044
20-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2723	2769	2815	2861	2907	2953	2999	3045
20-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2724	2770	2816	2862	2908	2954	3000	3046
20-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2725	2771	2817	2863	2909	2955	3001	3047
20-40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2726	2772	2818	2864	2910	2956	3002	3048
40-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2727	2773	2819	2865	2911	2957	3003	3049
40-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2728	2774	2820	2866	2912	2958	3004	3050
40-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2729	2775	2821	2867	2913	2959	3005	3051
40-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2730	2776	2822	2868	2914	2960	3006	3052
40-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2731	2777	2823	2869	2915	2961	3007	3053
40-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2732	2778	2824	2870	2916	2962	3008	3054
40-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2733	2779	2825	2871	2917	2963	3009	3055
40-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2734	2780	2826	2872	2918	2964	3010	3056
60-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2735	2781	2827	2873	2919	2965	3011	3057
60-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2736	2782	2828	2874	2920	2966	3012	3058
60-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2737	2783	2829	2875	2921	2967	3013	3059
60-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2738	2784	2830	2876	2922	2968	3014	3060
60-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2739	2785	2831	2877	2923	2969	3015	3061
60-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2740	2786	2832	2878	2924	2970	3016	3062
70-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2741	2787	2833	2879	2925	2971	3017	3063
70-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2742	2788	2834	2880	2926	2972	3018	3064
70-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2743	2789	2835	2881	2927	2973	3019	3065
70-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2744	2790	2836	2887	2928	2974	3020	3066

TABLE 14-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	1-8 hr	1-7 hr	1-6 hr	1-5 hr	1-4 hr	1-3 hr	1-2 hr	2-8 hr
70-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2745	2791	2837	2883	2929	2975	3021	3067
80-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2746	2792	2838	2884	2930	2976	3022	3068
80-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2747	2793	2839	2885	2931	2977	3023	3069
80-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2748	2794	2840	2886	2932	2978	3024	3070
80-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2749	2795	2841	2887	2933	2979	3025	3071
90-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2750	2796	2842	2888	2934	2980	3026	3072
90-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2751	2797	2843	2889	2935	2981	3027	3073
90-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	2752	2798	2844	2890	2936	2982	3028	3074

Var. = Variation

TABLE 15

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	2-7 hr	2-6 hr	2-5 hr	2-4 hr	2-3 hr	3-8 hr	3-7 hr	3-6 hr
(mU/ μ g)								
at least 20	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3075	3121	3167	3213	3259	3305	3351	3397
at least 30	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3076	3122	3168	3214	3260	3306	3352	3398
at least 40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3077	3123	3169	3215	3261	3307	3353	3399
at least 50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3078	3124	3170	3216	3262	3308	3354	3400
at least 60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3079	3125	3171	3217	3263	3309	3355	3401
at least 70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3080	3126	3172	3218	3264	3310	3356	3402
at least 80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3081	3127	3173	3219	3265	3311	3357	3403
at least 90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3082	3128	3174	3220	3266	3312	3358	3404
at least 100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3083	3129	3175	3221	3267	3313	3359	3405
at least 125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3084	3130	3176	3222	3268	3314	3360	3406
at least 150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3085	3131	3177	3223	3269	3315	3361	3407
20-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3086	3132	3178	3224	3270	3316	3362	3408
20-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3087	3133	3179	3225	3271	3317	3363	3409
20-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3088	3134	3180	3226	3272	3318	3364	3410
20-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3089	3135	3181	3227	3273	3319	3365	3411
20-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3090	3136	3182	3228	3274	3320	3366	3412
20-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3091	3137	3183	3229	3275	3321	3367	3413
20-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3092	3138	3184	3230	3276	3322	3368	3414
20-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3093	3139	3185	3231	3277	3323	3369	3415
20-40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3094	3140	3186	3232	3278	3324	3370	3416

TABLE 15-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	2-7 hr	2-6 hr	2-5 hr	2-4 hr	2-3 hr	3-8 hr	3-7 hr	3-6 hr
40-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3095	3141	3187	3233	3279	3325	3371	3417
40-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3096	3142	3188	3234	3280	3326	3372	3418
40-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3097	3143	3189	3235	3281	3327	3373	3419
40-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3098	3144	3190	3236	3282	3328	3374	3420
40-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3099	3145	3191	3237	3283	3329	3375	3421
40-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3100	3146	3192	3238	3284	3330	3376	3422
40-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3101	3147	3193	3239	3285	3331	3377	3423
40-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3102	3148	3194	3240	3286	3332	3378	3424
60-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3103	3149	3195	3241	3287	3333	3379	3425
60-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3104	3150	3196	3242	3288	3334	3380	3426
60-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3105	3151	3197	3243	3289	3335	3381	3427
60-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3106	3152	3198	3244	3290	3336	3382	3428
60-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3107	3153	3199	3245	3291	3337	3383	3429
60-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3108	3154	3200	3246	3292	3338	3384	3430
70-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3109	3155	3201	3247	3293	3339	3385	3431
70-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3110	3156	3202	3248	3294	3340	3386	3432
70-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3111	3157	3203	3249	3295	3341	3387	3433
70-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3112	3158	3204	3250	3296	3342	3388	3434
70-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3113	3159	3205	3251	3297	3343	3389	3435
80-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3114	3160	3206	3252	3298	3344	3390	3436
80-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3115	3161	3207	3253	3299	3345	3391	3437
80-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3116	3162	3208	3254	3300	3346	3392	3438
80-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3117	3163	3209	3255	3301	3347	3393	3439
90-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3118	3164	3210	3256	3302	3348	3394	3440
90-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3119	3165	3211	3257	3303	3349	3395	3441
90-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3120	3166	3212	3258	3304	3350	3396	3442

Var. = Variation

TABLE 16

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	3-5 hr	3-4 hr	4-8 hr	4-7 hr	4-6 hr	4-5 hr	5-8 hr	5-7 hr
(mU/ μ g)								
at least 20	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3443	3489	3535	3581	3627	3673	3719	3765
at least 30	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3444	3490	3536	3582	3628	3674	3720	3766

TABLE 16-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	3-5 hr	3-4 hr	4-8 hr	4-7 hr	4-6 hr	4-5 hr	5-8 hr	5-7 hr
at least 40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3445	3491	3537	3583	3629	3675	3721	3767
at least 50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3446	3492	3538	3584	3630	3676	3722	3768
at least 60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3447	3493	3539	3585	3631	3677	3723	3769
at least 70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3448	3494	3540	3586	3632	3678	3724	3770
at least 80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3449	3495	3541	3587	3633	3679	3725	3771
at least 90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3450	3496	3542	3588	3634	3680	3726	3772
at least 100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3451	3497	3543	3589	3635	3681	3727	3773
at least 125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3452	3498	3544	3590	3636	3682	3728	3774
at least 150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3453	3499	3545	3591	3637	3683	3729	3775
20-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3454	3500	3546	3592	3638	3684	3730	3776
20-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3455	3501	3547	3593	3639	3685	3731	3777
20-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3456	3502	3548	3594	3640	3686	3732	3778
20-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3457	3503	3549	3595	3641	3687	3733	3779
20-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3458	3504	3550	3596	3642	3688	3734	3780
20-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3459	3505	3551	3597	3643	3689	3735	3781
20-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3460	3506	3552	3598	3644	3690	3736	3782
20-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3461	3507	3553	3599	3645	3691	3737	3783
20-40	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3462	3508	3554	3600	3646	3692	3738	3784
40-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3463	3509	3555	3601	3647	3693	3739	3785
40-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3464	3510	3556	3602	3648	3694	3740	3786
40-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3465	3511	3557	3603	3649	3695	3741	3787
40-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3466	3512	3558	3604	3650	3696	3742	3788
40-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3467	3513	3559	3605	3651	3697	3743	3789
40-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3468	3514	3560	3606	3652	3698	3744	3790
40-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3469	3515	3561	3607	3653	3699	3745	3791
40-50	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3470	3516	3562	3608	3654	3700	3746	3792
60-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3471	3517	3563	3609	3655	3701	3747	3793
60-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3472	3518	3564	3610	3656	3702	3748	3794
60-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3473	3519	3565	3611	3657	3703	3749	3795
60-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3474	3520	3566	3612	3658	3704	3750	3796
60-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3475	3521	3567	3613	3659	3705	3751	3797
60-70	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3476	3522	3568	3614	3660	3706	3752	3798
70-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3477	3523	3569	3615	3661	3707	3753	3799
70-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3478	3524	3570	3616	3662	3708	3754	3800
70-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3479	3525	3571	3617	3663	3709	3755	3801
70-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3480	3526	3572	3618	3664	3710	3756	3802

TABLE 16-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	3-5 hr	3-4 hr	4-8 hr	4-7 hr	4-6 hr	4-5 hr	5-8 hr	5-7 hr
70-80	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3481	3527	3573	3619	3665	3711	3757	3803
80-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3482	3528	3574	3620	3666	3712	3758	3804
80-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3483	3529	3575	3621	3667	3713	3759	3805
80-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3484	3530	3576	3622	3668	3714	3760	3806
80-90	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3485	3531	3577	3623	3669	3715	3761	3807
90-150	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3486	3532	3578	3624	3670	3716	3762	3808
90-125	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3487	3533	3579	3625	3671	3717	3763	3809
90-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.
	3488	3534	3580	3626	3672	3718	3764	3810

Var. = Variation

TABLE 17

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)				Increased Stability (Percent)				
	5-6 hr	6-8 hr	6-7 hr	7-8 hr	at least 10%	at least 20%	at least 30%	at least 40%
(mU/ μ g)								
at least 20	Var.	Var.	Var.	Var.	Var. 3995	Var. 4041	Var. 4087	Var. 4133
	3811	3857	3903	3949				
at least 30	Var.	Var.	Var.	Var.	Var. 3996	Var. 4042	Var. 4088	Var. 4134
	3812	3858	3904	3950				
at least 40	Var.	Var.	Var.	Var.	Var. 3997	Var. 4043	Var. 4089	Var. 4135
	3813	3859	3905	3951				
at least 50	Var.	Var.	Var.	Var.	Var. 3998	Var. 4044	Var. 4090	Var. 4136
	3814	3860	3906	3952				
at least 60	Var.	Var.	Var.	Var.	Var. 3999	Var. 4045	Var. 4091	Var. 4137
	3815	3861	3907	3953				
at least 70	Var.	Var.	Var.	Var.	Var. 4000	Var. 4046	Var. 4092	Var. 4138
	3816	3862	3908	3954				
at least 80	Var.	Var.	Var.	Var.	Var. 4001	Var. 4047	Var. 4093	Var. 4139
	3817	3863	3909	3955				
at least 90	Var.	Var.	Var.	Var.	Var. 4002	Var. 4048	Var. 4094	Var. 4140
	3818	3864	3910	3956				
at least 100	Var.	Var.	Var.	Var.	Var. 4003	Var. 4049	Var. 4095	Var. 4141
	3819	3865	3911	3957				
at least 125	Var.	Var.	Var.	Var.	Var. 4004	Var. 4050	Var. 4096	Var. 4142
	3820	3866	3912	3958				
at least 150	Var.	Var.	Var.	Var.	Var. 4005	Var. 4051	Var. 4097	Var. 4143
	3821	3867	3913	3959				
20-150	Var.	Var.	Var.	Var.	Var. 4006	Var. 4052	Var. 4098	Var. 4144
	3822	3868	3914	3960				
20-125	Var.	Var.	Var.	Var.	Var. 4007	Var. 4053	Var. 4099	Var. 4145
	3823	3869	3915	3961				
20-100	Var.	Var.	Var.	Var.	Var. 4008	Var. 4054	Var. 4100	Var. 4146
	3824	3870	3916	3962				
20-90	Var.	Var.	Var.	Var.	Var. 4009	Var. 4055	Var. 4101	Var. 4147
	3825	3871	3917	3963				
20-80	Var.	Var.	Var.	Var.	Var. 4010	Var. 4056	Var. 4102	Var. 4148
	3826	3872	3918	3964				
20-70	Var.	Var.	Var.	Var.	Var. 4011	Var. 4057	Var. 4103	Var. 4149
	3827	3873	3919	3965				
20-60	Var.	Var.	Var.	Var.	Var. 4012	Var. 4058	Var. 4104	Var. 4150
	3828	3874	3920	3966				
20-50	Var.	Var.	Var.	Var.	Var. 4013	Var. 4059	Var. 4105	Var. 4151
	3829	3875	3921	3967				

TABLE 17-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
					Increased Stability (Percent)			
Increased Stability (Hours)					at least	at least	at least	at least
5-6 hr	6-8 hr	6-7 hr	7-8 hr		10%	20%	30%	40%
20-40	Var. 3830	Var. 3876	Var. 3922	Var. 3968	Var. 4014	Var. 4060	Var. 4106	Var. 4152
40-150	Var. 3831	Var. 3877	Var. 3923	Var. 3969	Var. 4015	Var. 4061	Var. 4107	Var. 4153
40-125	Var. 3832	Var. 3878	Var. 3924	Var. 3970	Var. 4016	Var. 4062	Var. 4108	Var. 4154
40-100	Var. 3833	Var. 3879	Var. 3925	Var. 3971	Var. 4017	Var. 4063	Var. 4109	Var. 4155
40-90	Var. 3834	Var. 3880	Var. 3926	Var. 3972	Var. 4018	Var. 4064	Var. 4110	Var. 4156
40-80	Var. 3835	Var. 3881	Var. 3927	Var. 3973	Var. 4019	Var. 4065	Var. 4111	Var. 4157
40-70	Var. 3836	Var. 3882	Var. 3928	Var. 3974	Var. 4020	Var. 4066	Var. 4112	Var. 4158
40-60	Var. 3837	Var. 3883	Var. 3929	Var. 3975	Var. 4021	Var. 4067	Var. 4113	Var. 4159
40-50	Var. 3838	Var. 3884	Var. 3930	Var. 3976	Var. 4022	Var. 4068	Var. 4114	Var. 4160
60-150	Var. 3839	Var. 3885	Var. 3931	Var. 3977	Var. 4023	Var. 4069	Var. 4115	Var. 4161
60-125	Var. 3840	Var. 3886	Var. 3932	Var. 3978	Var. 4024	Var. 4070	Var. 4116	Var. 4162
60-100	Var. 3841	Var. 3887	Var. 3933	Var. 3979	Var. 4025	Var. 4071	Var. 4117	Var. 4163
60-90	Var. 3842	Var. 3888	Var. 3934	Var. 3980	Var. 4026	Var. 4072	Var. 4118	Var. 4164
60-80	Var. 3843	Var. 3889	Var. 3935	Var. 3981	Var. 4027	Var. 4073	Var. 4119	Var. 4165
60-70	Var. 3844	Var. 3890	Var. 3936	Var. 3982	Var. 4028	Var. 4074	Var. 4120	Var. 4166
70-150	Var. 3845	Var. 3891	Var. 3937	Var. 3983	Var. 4029	Var. 4075	Var. 4121	Var. 4167
70-125	Var. 3846	Var. 3892	Var. 3938	Var. 3984	Var. 4030	Var. 4076	Var. 4122	Var. 4168
70-100	Var. 3847	Var. 3893	Var. 3939	Var. 3985	Var. 4031	Var. 4077	Var. 4123	Var. 4169
70-90	Var. 3848	Var. 3894	Var. 3940	Var. 3986	Var. 4032	Var. 4078	Var. 4124	Var. 4170
70-80	Var. 3849	Var. 3895	Var. 3941	Var. 3987	Var. 4033	Var. 4079	Var. 4125	Var. 4171
80-150	Var. 3850	Var. 3896	Var. 3942	Var. 3988	Var. 4034	Var. 4080	Var. 4126	Var. 4172
80-125	Var. 3851	Var. 3897	Var. 3943	Var. 3989	Var. 4035	Var. 4081	Var. 4127	Var. 4173
80-100	Var. 3852	Var. 3898	Var. 3944	Var. 3990	Var. 4036	Var. 4082	Var. 4128	Var. 4174
80-90	Var. 3853	Var. 3899	Var. 3945	Var. 3991	Var. 4037	Var. 4083	Var. 4129	Var. 4175
90-150	Var. 3854	Var. 3900	Var. 3946	Var. 3992	Var. 4038	Var. 4084	Var. 4130	Var. 4176
90-125	Var. 3855	Var. 3901	Var. 3947	Var. 3993	Var. 4039	Var. 4085	Var. 4131	Var. 4177
90-100	Var. 3856	Var. 3902	Var. 3948	Var. 3994	Var. 4040	Var. 4086	Var. 4132	Var. 4178

Var. = Variation

TABLE 18

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.									
Increased Stability (Percent)									
		at least 50%	10-50%	10-40%	10-30%	10-20%	15-50%	15-40%	15-30%
(mU/μg)	at least 20	Var. 4179	Var. 4225	Var. 4271	Var. 4317	Var. 4363	Var. 4409	Var. 4455	Var. 4501
	at least 30	Var. 4180	Var. 4226	Var. 4272	Var. 4318	Var. 4364	Var. 4410	Var. 4456	Var. 4502
	at least 40	Var. 4181	Var. 4227	Var. 4273	Var. 4319	Var. 4365	Var. 4411	Var. 4457	Var. 4503
	at least 50	Var. 4182	Var. 4228	Var. 4274	Var. 4320	Var. 4366	Var. 4412	Var. 4458	Var. 4504
	at least 60	Var. 4183	Var. 4229	Var. 4275	Var. 4321	Var. 4367	Var. 4413	Var. 4459	Var. 4505
	at least 70	Var. 4184	Var. 4230	Var. 4276	Var. 4322	Var. 4368	Var. 4414	Var. 4460	Var. 4506
	at least 80	Var. 4185	Var. 4231	Var. 4277	Var. 4323	Var. 4369	Var. 4415	Var. 4461	Var. 4507
	at least 90	Var. 4186	Var. 4232	Var. 4278	Var. 4324	Var. 4370	Var. 4416	Var. 4462	Var. 4508
	at least 100	Var. 4187	Var. 4233	Var. 4279	Var. 4325	Var. 4371	Var. 4417	Var. 4463	Var. 4509
	at least 125	Var. 4188	Var. 4234	Var. 4280	Var. 4326	Var. 4372	Var. 4418	Var. 4464	Var. 4510
	at least 150	Var. 4189	Var. 4235	Var. 4281	Var. 4327	Var. 4373	Var. 4419	Var. 4465	Var. 4511
	20-150	Var. 4190	Var. 4236	Var. 4282	Var. 4328	Var. 4374	Var. 4420	Var. 4466	Var. 4512
	20-125	Var. 4191	Var. 4237	Var. 4283	Var. 4329	Var. 4375	Var. 4421	Var. 4467	Var. 4513
	20-100	Var. 4192	Var. 4238	Var. 4284	Var. 4330	Var. 4376	Var. 4422	Var. 4468	Var. 4514
	20-90	Var. 4193	Var. 4239	Var. 4285	Var. 4331	Var. 4377	Var. 4423	Var. 4469	Var. 4515
	20-80	Var. 4194	Var. 4240	Var. 4286	Var. 4332	Var. 4378	Var. 4424	Var. 4470	Var. 4516
	20-70	Var. 4195	Var. 4241	Var. 4287	Var. 4333	Var. 4379	Var. 4425	Var. 4471	Var. 4517
	20-60	Var. 4196	Var. 4242	Var. 4288	Var. 4334	Var. 4380	Var. 4426	Var. 4472	Var. 4518
	20-50	Var. 4197	Var. 4243	Var. 4289	Var. 4335	Var. 4381	Var. 4427	Var. 4473	Var. 4519
	20-40	Var. 4198	Var. 4244	Var. 4290	Var. 4336	Var. 4382	Var. 4428	Var. 4474	Var. 4520
	40-150	Var. 4199	Var. 4245	Var. 4291	Var. 4337	Var. 4383	Var. 4429	Var. 4475	Var. 4521
	40-125	Var. 4200	Var. 4246	Var. 4292	Var. 4338	Var. 4384	Var. 4430	Var. 4476	Var. 4522
	40-100	Var. 4201	Var. 4247	Var. 4293	Var. 4339	Var. 4385	Var. 4431	Var. 4477	Var. 4523
	40-90	Var. 4202	Var. 4248	Var. 4294	Var. 4340	Var. 4386	Var. 4432	Var. 4478	Var. 4524
	40-80	Var. 4203	Var. 4249	Var. 4295	Var. 4341	Var. 4387	Var. 4433	Var. 4479	Var. 4525
	40-70	Var. 4204	Var. 4250	Var. 4296	Var. 4342	Var. 4388	Var. 4434	Var. 4480	Var. 4526
	40-60	Var. 4205	Var. 4251	Var. 4297	Var. 4343	Var. 4389	Var. 4435	Var. 4481	Var. 4527
	40-50	Var. 4206	Var. 4252	Var. 4298	Var. 4344	Var. 4390	Var. 4436	Var. 4482	Var. 4528
	60-150	Var. 4207	Var. 4253	Var. 4299	Var. 4345	Var. 4391	Var. 4437	Var. 4483	Var. 4529
	60-125	Var. 4208	Var. 4254	Var. 4300	Var. 4346	Var. 4392	Var. 4438	Var. 4484	Var. 4530
	60-100	Var. 4209	Var. 4255	Var. 4301	Var. 4347	Var. 4393	Var. 4439	Var. 4485	Var. 4531
	60-90	Var. 4210	Var. 4256	Var. 4302	Var. 4348	Var. 4394	Var. 4440	Var. 4486	Var. 4532
	60-80	Var. 4211	Var. 4257	Var. 4303	Var. 4349	Var. 4395	Var. 4441	Var. 4487	Var. 4533
	60-70	Var. 4212	Var. 4258	Var. 4304	Var. 4350	Var. 4396	Var. 4442	Var. 4488	Var. 4534
	70-150	Var. 4213	Var. 4259	Var. 4305	Var. 4351	Var. 4397	Var. 4443	Var. 4489	Var. 4535
	70-125	Var. 4214	Var. 4260	Var. 4306	Var. 4352	Var. 4398	Var. 4444	Var. 4490	Var. 4536

TABLE 18-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Percent)								
	at least 50%	10-50%	10-40%	10-30%	10-20%	15-50%	15-40%	15-30%
70-100	Var. 4215	Var. 4261	Var. 4307	Var. 4353	Var. 4399	Var. 4445	Var. 4491	Var. 4537
70-90	Var. 4216	Var. 4262	Var. 4308	Var. 4354	Var. 4400	Var. 4446	Var. 4492	Var. 4538
70-80	Var. 4217	Var. 4263	Var. 4309	Var. 4355	Var. 4401	Var. 4447	Var. 4493	Var. 4539
80-150	Var. 4218	Var. 4264	Var. 4310	Var. 4356	Var. 4402	Var. 4448	Var. 4494	Var. 4540
80-125	Var. 4219	Var. 4265	Var. 4311	Var. 4357	Var. 4403	Var. 4449	Var. 4495	Var. 4541
80-100	Var. 4220	Var. 4266	Var. 4312	Var. 4358	Var. 4404	Var. 4450	Var. 4496	Var. 4542
80-90	Var. 4221	Var. 4267	Var. 4313	Var. 4359	Var. 4405	Var. 4451	Var. 4497	Var. 4543
90-150	Var. 4222	Var. 4268	Var. 4314	Var. 4360	Var. 4406	Var. 4452	Var. 4498	Var. 4544
90-125	Var. 4223	Var. 4269	Var. 4315	Var. 4361	Var. 4407	Var. 4453	Var. 4499	Var. 4545
90-100	Var. 4224	Var. 4270	Var. 4316	Var. 4362	Var. 4408	Var. 4454	Var. 4500	Var. 4546

Var. = Variation

TABLE 19

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Percent)								
	15-20%	20-50%	20-40%	20-30%	30-50%	30-40%	40-50%	
(mU/μg)	at least 20	Var. 4547	Var. 4593	Var. 4639	Var. 4685	Var. 4731	Var. 4777	Var. 4823
	at least 30	Var. 4548	Var. 4594	Var. 4640	Var. 4686	Var. 4732	Var. 4778	Var. 4824
	at least 40	Var. 4549	Var. 4595	Var. 4641	Var. 4687	Var. 4733	Var. 4779	Var. 4825
	at least 50	Var. 4550	Var. 4596	Var. 4642	Var. 4688	Var. 4734	Var. 4780	Var. 4826
	at least 60	Var. 4551	Var. 4597	Var. 4643	Var. 4689	Var. 4735	Var. 4781	Var. 4827
	at least 70	Var. 4552	Var. 4598	Var. 4644	Var. 4690	Var. 4736	Var. 4782	Var. 4828
	at least 80	Var. 4553	Var. 4599	Var. 4645	Var. 4691	Var. 4737	Var. 4783	Var. 4829
	at least 90	Var. 4554	Var. 4600	Var. 4646	Var. 4692	Var. 4738	Var. 4784	Var. 4830
	at least 100	Var. 4555	Var. 4601	Var. 4647	Var. 4693	Var. 4739	Var. 4785	Var. 4831
	at least 125	Var. 4556	Var. 4602	Var. 4648	Var. 4694	Var. 4740	Var. 4786	Var. 4832
	at least 150	Var. 4557	Var. 4603	Var. 4649	Var. 4695	Var. 4741	Var. 4787	Var. 4833
	20-150	Var. 4558	Var. 4604	Var. 4650	Var. 4696	Var. 4742	Var. 4788	Var. 4834
	20-125	Var. 4559	Var. 4605	Var. 4651	Var. 4697	Var. 4743	Var. 4789	Var. 4835
	20-100	Var. 4560	Var. 4606	Var. 4652	Var. 4698	Var. 4744	Var. 4790	Var. 4836
	20-90	Var. 4561	Var. 4607	Var. 4653	Var. 4699	Var. 4745	Var. 4791	Var. 4837
	20-80	Var. 4562	Var. 4608	Var. 4654	Var. 4700	Var. 4746	Var. 4792	Var. 4838
	20-70	Var. 4563	Var. 4609	Var. 4655	Var. 4701	Var. 4747	Var. 4793	Var. 4839
	20-60	Var. 4564	Var. 4610	Var. 4656	Var. 4702	Var. 4748	Var. 4794	Var. 4840
	20-50	Var. 4565	Var. 4611	Var. 4657	Var. 4703	Var. 4749	Var. 4795	Var. 4841
	20-40	Var. 4566	Var. 4612	Var. 4658	Var. 4704	Var. 4750	Var. 4796	Var. 4842
	40-150	Var. 4567	Var. 4613	Var. 4659	Var. 4705	Var. 4751	Var. 4797	Var. 4843
	40-125	Var. 4568	Var. 4614	Var. 4660	Var. 4706	Var. 4752	Var. 4798	Var. 4844
	40-100	Var. 4569	Var. 4615	Var. 4661	Var. 4707	Var. 4753	Var. 4799	Var. 4845
	40-90	Var. 4570	Var. 4616	Var. 4662	Var. 4708	Var. 4754	Var. 4800	Var. 4846
	40-80	Var. 4571	Var. 4617	Var. 4663	Var. 4709	Var. 4755	Var. 4801	Var. 4847
	40-70	Var. 4572	Var. 4618	Var. 4664	Var. 4710	Var. 4756	Var. 4802	Var. 4848
	40-60	Var. 4573	Var. 4619	Var. 4665	Var. 4711	Var. 4757	Var. 4803	Var. 4849
	40-50	Var. 4574	Var. 4620	Var. 4666	Var. 4712	Var. 4758	Var. 4804	Var. 4850
	60-150	Var. 4575	Var. 4621	Var. 4667	Var. 4713	Var. 4759	Var. 4805	Var. 4851
	60-125	Var. 4576	Var. 4622	Var. 4668	Var. 4714	Var. 4760	Var. 4806	Var. 4852
	60-100	Var. 4577	Var. 4623	Var. 4669	Var. 4715	Var. 4761	Var. 4807	Var. 4853
	60-90	Var. 4578	Var. 4624	Var. 4670	Var. 4716	Var. 4762	Var. 4808	Var. 4854
	60-80	Var. 4579	Var. 4625	Var. 4671	Var. 4717	Var. 4763	Var. 4809	Var. 4855
	60-70	Var. 4580	Var. 4626	Var. 4672	Var. 4718	Var. 4764	Var. 4810	Var. 4856
	70-150	Var. 4581	Var. 4627	Var. 4673	Var. 4719	Var. 4765	Var. 4811	Var. 4857
	70-125	Var. 4582	Var. 4628	Var. 4674	Var. 4720	Var. 4766	Var. 4812	Var. 4858
	70-100	Var. 4583	Var. 4629	Var. 4675	Var. 4721	Var. 4767	Var. 4813	Var. 4859

TABLE 19-continued

Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Percent)							
	15-20%	20-50%	20-40%	20-30%	30-50%	30-40%	40-50%
70-90	Var. 4584	Var. 4630	Var. 4676	Var. 4722	Var. 4768	Var. 4814	Var. 4860
70-80	Var. 4585	Var. 4631	Var. 4677	Var. 4723	Var. 4769	Var. 4815	Var. 4861
80-150	Var. 4586	Var. 4632	Var. 4678	Var. 4724	Var. 4770	Var. 4816	Var. 4862
80-125	Var. 4587	Var. 4633	Var. 4679	Var. 4725	Var. 4771	Var. 4817	Var. 4863
80-100	Var. 4588	Var. 4634	Var. 4680	Var. 4726	Var. 4772	Var. 4818	Var. 4864
80-90	Var. 4589	Var. 4635	Var. 4681	Var. 4727	Var. 4773	Var. 4819	Var. 4865
90-150	Var. 4590	Var. 4636	Var. 4682	Var. 4728	Var. 4774	Var. 4820	Var. 4866
90-125	Var. 4591	Var. 4637	Var. 4683	Var. 4729	Var. 4775	Var. 4821	Var. 4867
90-100	Var. 4592	Var. 4638	Var. 4684	Var. 4730	Var. 4776	Var. 4822	Var. 4868

Var. = Variation

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one

embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 10 IU/kg to 40 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the composition contains from 20 IU/kg to 30 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 25 IU/kg to 75 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific

embodiment, the composition contains from 40 IU/kg to 60 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 75 IU/kg to 125 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the composition contains from 75 IU/kg to 100 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the subject is administered a dose of rVWF selected from variations 2141 to 2338 in Table 12, and wherein the combination of rVWF specific activity in

the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

TABLE 20

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
		at least 1 hr	at least 2 hr	at least 3 hr	at least 4 hr	at least 5 hr	at least 6 hr	at least 7 hr
Dosage	0.5-200	Var. 4869	Var. 4926	Var. 4983	Var. 5040	Var. 5097	Var. 5154	Var. 5211
(IU/kg	0.5-150	Var. 4870	Var. 4927	Var. 4984	Var. 5041	Var. 5098	Var. 5155	Var. 5212
rVWF:	0.5-100	Var. 4871	Var. 4928	Var. 4985	Var. 5042	Var. 5099	Var. 5156	Var. 5213
RCo	0.5-75	Var. 4872	Var. 4929	Var. 4986	Var. 5043	Var. 5100	Var. 5157	Var. 5214
activity)	0.5-50	Var. 4873	Var. 4930	Var. 4987	Var. 5044	Var. 5101	Var. 5158	Var. 5215
	0.5-25	Var. 4874	Var. 4931	Var. 4988	Var. 5045	Var. 5102	Var. 5159	Var. 5216
	0.5-10	Var. 4875	Var. 4932	Var. 4989	Var. 5046	Var. 5103	Var. 5160	Var. 5217
	0.5-5	Var. 4876	Var. 4933	Var. 4990	Var. 5047	Var. 5104	Var. 5161	Var. 5218
	0.5-2.5	Var. 4877	Var. 4934	Var. 4991	Var. 5048	Var. 5105	Var. 5162	Var. 5219
	0.5-1	Var. 4878	Var. 4935	Var. 4992	Var. 5049	Var. 5106	Var. 5163	Var. 5220
	2.5-200	Var. 4879	Var. 4936	Var. 4993	Var. 5050	Var. 5107	Var. 5164	Var. 5221
	2.5-150	Var. 4880	Var. 4937	Var. 4994	Var. 5051	Var. 5108	Var. 5165	Var. 5222
	2.5-100	Var. 4881	Var. 4938	Var. 4995	Var. 5052	Var. 5109	Var. 5166	Var. 5223
	2.5-75	Var. 4882	Var. 4939	Var. 4996	Var. 5053	Var. 5110	Var. 5167	Var. 5224
	2.5-50	Var. 4883	Var. 4940	Var. 4997	Var. 5054	Var. 5111	Var. 5168	Var. 5225
	2.5-25	Var. 4884	Var. 4941	Var. 4998	Var. 5055	Var. 5112	Var. 5169	Var. 5226
	2.5-10	Var. 4885	Var. 4942	Var. 4999	Var. 5056	Var. 5113	Var. 5170	Var. 5227
	2.5-5	Var. 4886	Var. 4943	Var. 5000	Var. 5057	Var. 5114	Var. 5171	Var. 5228
	5-200	Var. 4887	Var. 4944	Var. 5001	Var. 5058	Var. 5115	Var. 5172	Var. 5229
	5-175	Var. 4888	Var. 4945	Var. 5002	Var. 5059	Var. 5116	Var. 5173	Var. 5230
	5-150	Var. 4889	Var. 4946	Var. 5003	Var. 5060	Var. 5117	Var. 5174	Var. 5231
	5-125	Var. 4890	Var. 4947	Var. 5004	Var. 5061	Var. 5118	Var. 5175	Var. 5232
	5-100	Var. 4891	Var. 4948	Var. 5005	Var. 5062	Var. 5119	Var. 5176	Var. 5233
	5-75	Var. 4892	Var. 4949	Var. 5006	Var. 5063	Var. 5120	Var. 5177	Var. 5234
	5-50	Var. 4893	Var. 4950	Var. 5007	Var. 5064	Var. 5121	Var. 5178	Var. 5235
	5-25	Var. 4894	Var. 4951	Var. 5008	Var. 5065	Var. 5122	Var. 5179	Var. 5236
	5-10	Var. 4895	Var. 4952	Var. 5009	Var. 5066	Var. 5123	Var. 5180	Var. 5237
	10-200	Var. 4896	Var. 4953	Var. 5010	Var. 5067	Var. 5124	Var. 5181	Var. 5238
	10-150	Var. 4897	Var. 4954	Var. 5011	Var. 5068	Var. 5125	Var. 5182	Var. 5239
	10-100	Var. 4898	Var. 4955	Var. 5012	Var. 5069	Var. 5126	Var. 5183	Var. 5240
	10-75	Var. 4899	Var. 4956	Var. 5013	Var. 5070	Var. 5127	Var. 5184	Var. 5241
	10-50	Var. 4900	Var. 4957	Var. 5014	Var. 5071	Var. 5128	Var. 5185	Var. 5242
	10-25	Var. 4901	Var. 4958	Var. 5015	Var. 5072	Var. 5129	Var. 5186	Var. 5243
	25-200	Var. 4902	Var. 4959	Var. 5016	Var. 5073	Var. 5130	Var. 5187	Var. 5244
	25-150	Var. 4903	Var. 4960	Var. 5017	Var. 5074	Var. 5131	Var. 5188	Var. 5245

TABLE 20-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Hours)							
	at least 1 hr	at least 2 hr	at least 3 hr	at least 4 hr	at least 5 hr	at least 6 hr	at least 7 hr
25-100	Var. 4904	Var. 4961	Var. 5018	Var. 5075	Var. 5132	Var. 5189	Var. 5246
25-75	Var. 4905	Var. 4962	Var. 5019	Var. 5076	Var. 5133	Var. 5190	Var. 5247
25-50	Var. 4906	Var. 4963	Var. 5020	Var. 5077	Var. 5134	Var. 5191	Var. 5248
50-200	Var. 4907	Var. 4964	Var. 5021	Var. 5078	Var. 5135	Var. 5192	Var. 5249
50-150	Var. 4908	Var. 4965	Var. 5022	Var. 5079	Var. 5136	Var. 5193	Var. 5250
50-100	Var. 4909	Var. 4966	Var. 5023	Var. 5080	Var. 5137	Var. 5194	Var. 5251
50-75	Var. 4910	Var. 4967	Var. 5024	Var. 5081	Var. 5138	Var. 5195	Var. 5252
75-200	Var. 4911	Var. 4968	Var. 5025	Var. 5082	Var. 5139	Var. 5196	Var. 5253
75-175	Var. 4912	Var. 4969	Var. 5026	Var. 5083	Var. 5140	Var. 5197	Var. 5254
75-150	Var. 4913	Var. 4970	Var. 5027	Var. 5084	Var. 5141	Var. 5198	Var. 5255
75-125	Var. 4914	Var. 4971	Var. 5028	Var. 5085	Var. 5142	Var. 5199	Var. 5256
75-100	Var. 4915	Var. 4972	Var. 5029	Var. 5086	Var. 5143	Var. 5200	Var. 5257
100-200	Var. 4916	Var. 4973	Var. 5030	Var. 5087	Var. 5144	Var. 5201	Var. 5258
100-175	Var. 4917	Var. 4974	Var. 5031	Var. 5088	Var. 5145	Var. 5202	Var. 5259
100-150	Var. 4918	Var. 4975	Var. 5032	Var. 5089	Var. 5146	Var. 5203	Var. 5260
100-125	Var. 4919	Var. 4976	Var. 5033	Var. 5090	Var. 5147	Var. 5204	Var. 5261
125-200	Var. 4920	Var. 4977	Var. 5034	Var. 5091	Var. 5148	Var. 5205	Var. 5262
125-175	Var. 4921	Var. 4978	Var. 5035	Var. 5092	Var. 5149	Var. 5206	Var. 5263
125-150	Var. 4922	Var. 4979	Var. 5036	Var. 5093	Var. 5150	Var. 5207	Var. 5264
150-200	Var. 4923	Var. 4980	Var. 5037	Var. 5094	Var. 5151	Var. 5208	Var. 5265
150-200	Var. 4924	Var. 4981	Var. 5038	Var. 5095	Var. 5152	Var. 5209	Var. 5266
175-200	Var. 4925	Var. 4982	Var. 5039	Var. 5096	Var. 5153	Var. 5210	Var. 5267

Var. = Variation

TABLE 21

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	at least 8 hr	1-8 hr	1-7 hr	1-6 hr	1-5 hr	1-4 hr	1-3 hr	
Dosage	0.5-200	Var. 5268	Var. 5325	Var. 5382	Var. 5439	Var. 5496	Var. 5553	Var. 5610
(IU/kg	0.5-150	Var. 5269	Var. 5326	Var. 5383	Var. 5440	Var. 5497	Var. 5554	Var. 5611
rVWF:	0.5-100	Var. 5270	Var. 5327	Var. 5384	Var. 5441	Var. 5498	Var. 5555	Var. 5612
RCo	0.5-75	Var. 5271	Var. 5328	Var. 5385	Var. 5442	Var. 5499	Var. 5556	Var. 5613
activity)	0.5-50	Var. 5272	Var. 5329	Var. 5386	Var. 5443	Var. 5500	Var. 5557	Var. 5614
	0.5-25	Var. 5273	Var. 5330	Var. 5387	Var. 5444	Var. 5501	Var. 5558	Var. 5615
	0.5-10	Var. 5274	Var. 5331	Var. 5388	Var. 5445	Var. 5502	Var. 5559	Var. 5616
	0.5-5	Var. 5275	Var. 5332	Var. 5389	Var. 5446	Var. 5503	Var. 5560	Var. 5617
	0.5-2.5	Var. 5276	Var. 5333	Var. 5390	Var. 5447	Var. 5504	Var. 5561	Var. 5618
	0.5-1	Var. 5277	Var. 5334	Var. 5391	Var. 5448	Var. 5505	Var. 5562	Var. 5619
	2.5-200	Var. 5278	Var. 5335	Var. 5392	Var. 5449	Var. 5506	Var. 5563	Var. 5620
	2.5-150	Var. 5279	Var. 5336	Var. 5393	Var. 5450	Var. 5507	Var. 5564	Var. 5621
	2.5-100	Var. 5280	Var. 5337	Var. 5394	Var. 5451	Var. 5508	Var. 5565	Var. 5622
	2.5-75	Var. 5281	Var. 5338	Var. 5395	Var. 5452	Var. 5509	Var. 5566	Var. 5623
	2.5-50	Var. 5282	Var. 5339	Var. 5396	Var. 5453	Var. 5510	Var. 5567	Var. 5624
	2.5-25	Var. 5283	Var. 5340	Var. 5397	Var. 5454	Var. 5511	Var. 5568	Var. 5625
	2.5-10	Var. 5284	Var. 5341	Var. 5398	Var. 5455	Var. 5512	Var. 5569	Var. 5626
	2.5-5	Var. 5285	Var. 5342	Var. 5399	Var. 5456	Var. 5513	Var. 5570	Var. 5627
	5-200	Var. 5286	Var. 5343	Var. 5400	Var. 5457	Var. 5514	Var. 5571	Var. 5628
	5-175	Var. 5287	Var. 5344	Var. 5401	Var. 5458	Var. 5515	Var. 5572	Var. 5629
	5-150	Var. 5288	Var. 5345	Var. 5402	Var. 5459	Var. 5516	Var. 5573	Var. 5630
	5-125	Var. 5289	Var. 5346	Var. 5403	Var. 5460	Var. 5517	Var. 5574	Var. 5631
	5-100	Var. 5290	Var. 5347	Var. 5404	Var. 5461	Var. 5518	Var. 5575	Var. 5632
	5-75	Var. 5291	Var. 5348	Var. 5405	Var. 5462	Var. 5519	Var. 5576	Var. 5633
	5-50	Var. 5292	Var. 5349	Var. 5406	Var. 5463	Var. 5520	Var. 5577	Var. 5634
	5-25	Var. 5293	Var. 5350	Var. 5407	Var. 5464	Var. 5521	Var. 5578	Var. 5635
	5-10	Var. 5294	Var. 5351	Var. 5408	Var. 5465	Var. 5522	Var. 5579	Var. 5636
	10-200	Var. 5295	Var. 5352	Var. 5409	Var. 5466	Var. 5523	Var. 5580	Var. 5637
	10-150	Var. 5296	Var. 5353	Var. 5410	Var. 5467	Var. 5524	Var. 5581	Var. 5638
	10-100	Var. 5297	Var. 5354	Var. 5411	Var. 5468	Var. 5525	Var. 5582	Var. 5639
	10-75	Var. 5298	Var. 5355	Var. 5412	Var. 5469	Var. 5526	Var. 5583	Var. 5640
	10-50	Var. 5299	Var. 5356	Var. 5413	Var. 5470	Var. 5527	Var. 5584	Var. 5641
	10-25	Var. 5300	Var. 5357	Var. 5414	Var. 5471	Var. 5528	Var. 5585	Var. 5642
	25-200	Var. 5301	Var. 5358	Var. 5415	Var. 5472	Var. 5529	Var. 5586	Var. 5643
	25-150	Var. 5302	Var. 5359	Var. 5416	Var. 5473	Var. 5530	Var. 5587	Var. 5644
	25-100	Var. 5303	Var. 5360	Var. 5417	Var. 5474	Var. 5531	Var. 5588	Var. 5645
	25-75	Var. 5304	Var. 5361	Var. 5418	Var. 5475	Var. 5532	Var. 5589	Var. 5646

TABLE 21-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Hours)							
	at least 8 hr	1-8 hr	1-7 hr	1-6 hr	1-5 hr	1-4 hr	1-3 hr
25-50	Var. 5305	Var. 5362	Var. 5419	Var. 5476	Var. 5533	Var. 5590	Var. 5647
50-200	Var. 5306	Var. 5363	Var. 5420	Var. 5477	Var. 5534	Var. 5591	Var. 5648
50-150	Var. 5307	Var. 5364	Var. 5421	Var. 5478	Var. 5535	Var. 5592	Var. 5649
50-100	Var. 5308	Var. 5365	Var. 5422	Var. 5479	Var. 5536	Var. 5593	Var. 5650
50-75	Var. 5309	Var. 5366	Var. 5423	Var. 5480	Var. 5537	Var. 5594	Var. 5651
75-200	Var. 5310	Var. 5367	Var. 5424	Var. 5481	Var. 5538	Var. 5595	Var. 5652
75-175	Var. 5311	Var. 5368	Var. 5425	Var. 5482	Var. 5539	Var. 5596	Var. 5653
75-150	Var. 5312	Var. 5369	Var. 5426	Var. 5483	Var. 5540	Var. 5597	Var. 5654
75-125	Var. 5313	Var. 5370	Var. 5427	Var. 5484	Var. 5541	Var. 5598	Var. 5655
75-100	Var. 5314	Var. 5371	Var. 5428	Var. 5485	Var. 5542	Var. 5599	Var. 5656
100-200	Var. 5315	Var. 5372	Var. 5429	Var. 5486	Var. 5543	Var. 5600	Var. 5657
100-175	Var. 5316	Var. 5373	Var. 5430	Var. 5487	Var. 5544	Var. 5601	Var. 5658
100-150	Var. 5317	Var. 5374	Var. 5431	Var. 5488	Var. 5545	Var. 5602	Var. 5659
100-125	Var. 5318	Var. 5375	Var. 5432	Var. 5489	Var. 5546	Var. 5603	Var. 5660
125-200	Var. 5319	Var. 5376	Var. 5433	Var. 5490	Var. 5547	Var. 5604	Var. 5661
125-175	Var. 5320	Var. 5377	Var. 5434	Var. 5491	Var. 5548	Var. 5605	Var. 5662
125-150	Var. 5321	Var. 5378	Var. 5435	Var. 5492	Var. 5549	Var. 5606	Var. 5663
150-200	Var. 5322	Var. 5379	Var. 5436	Var. 5493	Var. 5550	Var. 5607	Var. 5664
150-200	Var. 5323	Var. 5380	Var. 5437	Var. 5494	Var. 5551	Var. 5608	Var. 5665
175-200	Var. 5324	Var. 5381	Var. 5438	Var. 5495	Var. 5552	Var. 5609	Var. 5666

Var. = Variation

TABLE 22

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
		1-2 hr	2-8 hr	2-7 hr	2-6 hr	2-5 hr	2-4 hr	2-3 hr
Dosage (IU/kg rVWF: RCo activity)	0.5-200	Var. 5667	Var. 5724	Var. 5781	Var. 5838	Var. 5895	Var. 5952	Var. 6009
	0.5-150	Var. 5668	Var. 5725	Var. 5782	Var. 5839	Var. 5896	Var. 5953	Var. 6010
	0.5-100	Var. 5669	Var. 5726	Var. 5783	Var. 5840	Var. 5897	Var. 5954	Var. 6011
	0.5-75	Var. 5670	Var. 5727	Var. 5784	Var. 5841	Var. 5898	Var. 5955	Var. 6012
	0.5-50	Var. 5671	Var. 5728	Var. 5785	Var. 5842	Var. 5899	Var. 5956	Var. 6013
	0.5-25	Var. 5672	Var. 5729	Var. 5786	Var. 5843	Var. 5900	Var. 5957	Var. 6014
	0.5-10	Var. 5673	Var. 5730	Var. 5787	Var. 5844	Var. 5901	Var. 5958	Var. 6015
	0.5-5	Var. 5674	Var. 5731	Var. 5788	Var. 5845	Var. 5902	Var. 5959	Var. 6016
	0.5-2.5	Var. 5675	Var. 5732	Var. 5789	Var. 5846	Var. 5903	Var. 5960	Var. 6017
	0.5-1	Var. 5676	Var. 5733	Var. 5790	Var. 5847	Var. 5904	Var. 5961	Var. 6018
	2.5-200	Var. 5677	Var. 5734	Var. 5791	Var. 5848	Var. 5905	Var. 5962	Var. 6019
	2.5-150	Var. 5678	Var. 5735	Var. 5792	Var. 5849	Var. 5906	Var. 5963	Var. 6020
	2.5-100	Var. 5679	Var. 5736	Var. 5793	Var. 5850	Var. 5907	Var. 5964	Var. 6021
	2.5-75	Var. 5680	Var. 5737	Var. 5794	Var. 5851	Var. 5908	Var. 5965	Var. 6022
	2.5-50	Var. 5681	Var. 5738	Var. 5795	Var. 5852	Var. 5909	Var. 5966	Var. 6023
	2.5-25	Var. 5682	Var. 5739	Var. 5796	Var. 5853	Var. 5910	Var. 5967	Var. 6024
	2.5-10	Var. 5683	Var. 5740	Var. 5797	Var. 5854	Var. 5911	Var. 5968	Var. 6025
	2.5-5	Var. 5684	Var. 5741	Var. 5798	Var. 5855	Var. 5912	Var. 5969	Var. 6026
	5-200	Var. 5685	Var. 5742	Var. 5799	Var. 5856	Var. 5913	Var. 5970	Var. 6027
	5-175	Var. 5686	Var. 5743	Var. 5800	Var. 5857	Var. 5914	Var. 5971	Var. 6028
	5-150	Var. 5687	Var. 5744	Var. 5801	Var. 5858	Var. 5915	Var. 5972	Var. 6029
	5-125	Var. 5688	Var. 5745	Var. 5802	Var. 5859	Var. 5916	Var. 5973	Var. 6030
	5-100	Var. 5689	Var. 5746	Var. 5803	Var. 5860	Var. 5917	Var. 5974	Var. 6031
	5-75	Var. 5690	Var. 5747	Var. 5804	Var. 5861	Var. 5918	Var. 5975	Var. 6032
	5-50	Var. 5691	Var. 5748	Var. 5805	Var. 5862	Var. 5919	Var. 5976	Var. 6033
	5-25	Var. 5692	Var. 5749	Var. 5806	Var. 5863	Var. 5920	Var. 5977	Var. 6034
	5-10	Var. 5693	Var. 5750	Var. 5807	Var. 5864	Var. 5921	Var. 5978	Var. 6035
	10-200	Var. 5694	Var. 5751	Var. 5808	Var. 5865	Var. 5922	Var. 5979	Var. 6036
	10-150	Var. 5695	Var. 5752	Var. 5809	Var. 5866	Var. 5923	Var. 5980	Var. 6037
	10-100	Var. 5696	Var. 5753	Var. 5810	Var. 5867	Var. 5924	Var. 5981	Var. 6038
	10-75	Var. 5697	Var. 5754	Var. 5811	Var. 5868	Var. 5925	Var. 5982	Var. 6039
	10-50	Var. 5698	Var. 5755	Var. 5812	Var. 5869	Var. 5926	Var. 5983	Var. 6040
	10-25	Var. 5699	Var. 5756	Var. 5813	Var. 5870	Var. 5927	Var. 5984	Var. 6041
	25-200	Var. 5700	Var. 5757	Var. 5814	Var. 5871	Var. 5928	Var. 5985	Var. 6042
	25-150	Var. 5701	Var. 5758	Var. 5815	Var. 5872	Var. 5929	Var. 5986	Var. 6043
	25-100	Var. 5702	Var. 5759	Var. 5816	Var. 5873	Var. 5930	Var. 5987	Var. 6044
	25-75	Var. 5703	Var. 5760	Var. 5817	Var. 5874	Var. 5931	Var. 5988	Var. 6045
	25-50	Var. 5704	Var. 5761	Var. 5818	Var. 5875	Var. 5932	Var. 5989	Var. 6046
	50-200	Var. 5705	Var. 5762	Var. 5819	Var. 5876	Var. 5933	Var. 5990	Var. 6047

TABLE 22-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Hours)							
	1-2 hr	2-8 hr	2-7 hr	2-6 hr	2-5 hr	2-4 hr	2-3 hr
50-150	Var. 5706	Var. 5763	Var. 5820	Var. 5877	Var. 5934	Var. 5991	Var. 6048
50-100	Var. 5707	Var. 5764	Var. 5821	Var. 5878	Var. 5935	Var. 5992	Var. 6049
50-75	Var. 5708	Var. 5765	Var. 5822	Var. 5879	Var. 5936	Var. 5993	Var. 6050
75-200	Var. 5709	Var. 5766	Var. 5823	Var. 5880	Var. 5937	Var. 5994	Var. 6051
75-175	Var. 5710	Var. 5767	Var. 5824	Var. 5881	Var. 5938	Var. 5995	Var. 6052
75-150	Var. 5711	Var. 5768	Var. 5825	Var. 5882	Var. 5939	Var. 5996	Var. 6053
75-125	Var. 5712	Var. 5769	Var. 5826	Var. 5883	Var. 5940	Var. 5997	Var. 6054
75-100	Var. 5713	Var. 5770	Var. 5827	Var. 5884	Var. 5941	Var. 5998	Var. 6055
100-200	Var. 5714	Var. 5771	Var. 5828	Var. 5885	Var. 5942	Var. 5999	Var. 6056
100-175	Var. 5715	Var. 5772	Var. 5829	Var. 5886	Var. 5943	Var. 6000	Var. 6057
100-150	Var. 5716	Var. 5773	Var. 5830	Var. 5887	Var. 5944	Var. 6001	Var. 6058
100-125	Var. 5717	Var. 5774	Var. 5831	Var. 5888	Var. 5945	Var. 6002	Var. 6059
125-200	Var. 5718	Var. 5775	Var. 5832	Var. 5889	Var. 5946	Var. 6003	Var. 6060
125-175	Var. 5719	Var. 5776	Var. 5833	Var. 5890	Var. 5947	Var. 6004	Var. 6061
125-150	Var. 5720	Var. 5777	Var. 5834	Var. 5891	Var. 5948	Var. 6005	Var. 6062
150-200	Var. 5721	Var. 5778	Var. 5835	Var. 5892	Var. 5949	Var. 6006	Var. 6063
150-200	Var. 5722	Var. 5779	Var. 5836	Var. 5893	Var. 5950	Var. 6007	Var. 6064
175-200	Var. 5723	Var. 5780	Var. 5837	Var. 5894	Var. 5951	Var. 6008	Var. 6065

Var. = Variation

TABLE 23

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	3-8 hr	3-7 hr	3-6 hr	3-5 hr	3-4 hr	4-8 hr	4-7 hr	
Dosage (IU/kg rVWF:RCo activity)	0.5-200	Var. 6066	Var. 6123	Var. 6180	Var. 6237	Var. 6294	Var. 6351	Var. 6408
	0.5-150	Var. 6067	Var. 6124	Var. 6181	Var. 6238	Var. 6295	Var. 6352	Var. 6409
	0.5-100	Var. 6068	Var. 6125	Var. 6182	Var. 6239	Var. 6296	Var. 6353	Var. 6410
	0.5-75	Var. 6069	Var. 6126	Var. 6183	Var. 6240	Var. 6297	Var. 6354	Var. 6411
	0.5-50	Var. 6070	Var. 6127	Var. 6184	Var. 6241	Var. 6298	Var. 6355	Var. 6412
	0.5-25	Var. 6071	Var. 6128	Var. 6185	Var. 6242	Var. 6299	Var. 6356	Var. 6413
	0.5-10	Var. 6072	Var. 6129	Var. 6186	Var. 6243	Var. 6300	Var. 6357	Var. 6414
	0.5-5	Var. 6073	Var. 6130	Var. 6187	Var. 6244	Var. 6301	Var. 6358	Var. 6415
	0.5-2.5	Var. 6074	Var. 6131	Var. 6188	Var. 6245	Var. 6302	Var. 6359	Var. 6416
	0.5-1	Var. 6075	Var. 6132	Var. 6189	Var. 6246	Var. 6303	Var. 6360	Var. 6417
	2.5-200	Var. 6076	Var. 6133	Var. 6190	Var. 6247	Var. 6304	Var. 6361	Var. 6418
	2.5-150	Var. 6077	Var. 6134	Var. 6191	Var. 6248	Var. 6305	Var. 6362	Var. 6419
	2.5-100	Var. 6078	Var. 6135	Var. 6192	Var. 6249	Var. 6306	Var. 6363	Var. 6420
	2.5-75	Var. 6079	Var. 6136	Var. 6193	Var. 6250	Var. 6307	Var. 6364	Var. 6421
	2.5-50	Var. 6080	Var. 6137	Var. 6194	Var. 6251	Var. 6308	Var. 6365	Var. 6422
	2.5-25	Var. 6081	Var. 6138	Var. 6195	Var. 6252	Var. 6309	Var. 6366	Var. 6423
	2.5-10	Var. 6082	Var. 6139	Var. 6196	Var. 6253	Var. 6310	Var. 6367	Var. 6424
	2.5-5	Var. 6083	Var. 6140	Var. 6197	Var. 6254	Var. 6311	Var. 6368	Var. 6425
	5-200	Var. 6084	Var. 6141	Var. 6198	Var. 6255	Var. 6312	Var. 6369	Var. 6426
	5-175	Var. 6085	Var. 6142	Var. 6199	Var. 6256	Var. 6313	Var. 6370	Var. 6427
	5-150	Var. 6086	Var. 6143	Var. 6200	Var. 6257	Var. 6314	Var. 6371	Var. 6428
	5-125	Var. 6087	Var. 6144	Var. 6201	Var. 6258	Var. 6315	Var. 6372	Var. 6429
	5-100	Var. 6088	Var. 6145	Var. 6202	Var. 6259	Var. 6316	Var. 6373	Var. 6430
	5-75	Var. 6089	Var. 6146	Var. 6203	Var. 6260	Var. 6317	Var. 6374	Var. 6431
	5-50	Var. 6090	Var. 6147	Var. 6204	Var. 6261	Var. 6318	Var. 6375	Var. 6432
	5-25	Var. 6091	Var. 6148	Var. 6205	Var. 6262	Var. 6319	Var. 6376	Var. 6433
	5-10	Var. 6092	Var. 6149	Var. 6206	Var. 6263	Var. 6320	Var. 6377	Var. 6434
	10-200	Var. 6093	Var. 6150	Var. 6207	Var. 6264	Var. 6321	Var. 6378	Var. 6435
	10-150	Var. 6094	Var. 6151	Var. 6208	Var. 6265	Var. 6322	Var. 6379	Var. 6436
	10-100	Var. 6095	Var. 6152	Var. 6209	Var. 6266	Var. 6323	Var. 6380	Var. 6437
	10-75	Var. 6096	Var. 6153	Var. 6210	Var. 6267	Var. 6324	Var. 6381	Var. 6438
	10-50	Var. 6097	Var. 6154	Var. 6211	Var. 6268	Var. 6325	Var. 6382	Var. 6439
	10-25	Var. 6098	Var. 6155	Var. 6212	Var. 6269	Var. 6326	Var. 6383	Var. 6440
	25-200	Var. 6099	Var. 6156	Var. 6213	Var. 6270	Var. 6327	Var. 6384	Var. 6441
	25-150	Var. 6100	Var. 6157	Var. 6214	Var. 6271	Var. 6328	Var. 6385	Var. 6442
	25-100	Var. 6101	Var. 6158	Var. 6215	Var. 6272	Var. 6329	Var. 6386	Var. 6443
	25-75	Var. 6102	Var. 6159	Var. 6216	Var. 6273	Var. 6330	Var. 6387	Var. 6444
	25-50	Var. 6103	Var. 6160	Var. 6217	Var. 6274	Var. 6331	Var. 6388	Var. 6445
	50-200	Var. 6104	Var. 6161	Var. 6218	Var. 6275	Var. 6332	Var. 6389	Var. 6446
	50-150	Var. 6105	Var. 6162	Var. 6219	Var. 6276	Var. 6333	Var. 6390	Var. 6447
	50-100	Var. 6106	Var. 6163	Var. 6220	Var. 6277	Var. 6334	Var. 6391	Var. 6448

TABLE 23-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	3-8 hr	3-7 hr	3-6 hr	3-5 hr	3-4 hr	4-8 hr	4-7 hr	
50-75	Var. 6107	Var. 6164	Var. 6221	Var. 6278	Var. 6335	Var. 6392	Var. 6449	
75-200	Var. 6108	Var. 6165	Var. 6222	Var. 6279	Var. 6336	Var. 6393	Var. 6450	
75-175	Var. 6109	Var. 6166	Var. 6223	Var. 6280	Var. 6337	Var. 6394	Var. 6451	
75-150	Var. 6110	Var. 6167	Var. 6224	Var. 6281	Var. 6338	Var. 6395	Var. 6452	
75-125	Var. 6111	Var. 6168	Var. 6225	Var. 6282	Var. 6339	Var. 6396	Var. 6453	
75-100	Var. 6112	Var. 6169	Var. 6226	Var. 6283	Var. 6340	Var. 6397	Var. 6454	
100-200	Var. 6113	Var. 6170	Var. 6227	Var. 6284	Var. 6341	Var. 6398	Var. 6455	
100-175	Var. 6114	Var. 6171	Var. 6228	Var. 6285	Var. 6342	Var. 6399	Var. 6456	
100-150	Var. 6115	Var. 6172	Var. 6229	Var. 6286	Var. 6343	Var. 6400	Var. 6457	
100-125	Var. 6116	Var. 6173	Var. 6230	Var. 6287	Var. 6344	Var. 6401	Var. 6458	
125-200	Var. 6117	Var. 6174	Var. 6231	Var. 6288	Var. 6345	Var. 6402	Var. 6459	
125-175	Var. 6118	Var. 6175	Var. 6232	Var. 6289	Var. 6346	Var. 6403	Var. 6460	
125-150	Var. 6119	Var. 6176	Var. 6233	Var. 6290	Var. 6347	Var. 6404	Var. 6461	
150-200	Var. 6120	Var. 6177	Var. 6234	Var. 6291	Var. 6348	Var. 6405	Var. 6462	
150-200	Var. 6121	Var. 6178	Var. 6235	Var. 6292	Var. 6349	Var. 6406	Var. 6463	
175-200	Var. 6122	Var. 6179	Var. 6236	Var. 6293	Var. 6350	Var. 6407	Var. 6464	

Var. = Variation

TABLE 24

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	4-6 hr	4-5 hr	5-8 hr	5-7 hr	5-6 hr	6-8 hr	6-7 hr	
Dosage	0.5-200	Var. 6465	Var. 6522	Var. 6579	Var. 6636	Var. 6693	Var. 6750	Var. 6807
(IU/kg rVWF:RCo	0.5-150	Var. 6466	Var. 6523	Var. 6580	Var. 6637	Var. 6694	Var. 6751	Var. 6808
activity)	0.5-100	Var. 6467	Var. 6524	Var. 6581	Var. 6638	Var. 6695	Var. 6752	Var. 6809
	0.5-75	Var. 6468	Var. 6525	Var. 6582	Var. 6639	Var. 6696	Var. 6753	Var. 6810
	0.5-50	Var. 6469	Var. 6526	Var. 6583	Var. 6640	Var. 6697	Var. 6754	Var. 6811
	0.5-25	Var. 6470	Var. 6527	Var. 6584	Var. 6641	Var. 6698	Var. 6755	Var. 6812
	0.5-10	Var. 6471	Var. 6528	Var. 6585	Var. 6642	Var. 6699	Var. 6756	Var. 6813
	0.5-5	Var. 6472	Var. 6529	Var. 6586	Var. 6643	Var. 6700	Var. 6757	Var. 6814
	0.5-2.5	Var. 6473	Var. 6530	Var. 6587	Var. 6644	Var. 6701	Var. 6758	Var. 6815
	0.5-1	Var. 6474	Var. 6531	Var. 6588	Var. 6645	Var. 6702	Var. 6759	Var. 6816
	2.5-200	Var. 6475	Var. 6532	Var. 6589	Var. 6646	Var. 6703	Var. 6760	Var. 6817
	2.5-150	Var. 6476	Var. 6533	Var. 6590	Var. 6647	Var. 6704	Var. 6761	Var. 6818
	2.5-100	Var. 6477	Var. 6534	Var. 6591	Var. 6648	Var. 6705	Var. 6762	Var. 6819
	2.5-75	Var. 6478	Var. 6535	Var. 6592	Var. 6649	Var. 6706	Var. 6763	Var. 6820
	2.5-50	Var. 6479	Var. 6536	Var. 6593	Var. 6650	Var. 6707	Var. 6764	Var. 6821
	2.5-25	Var. 6480	Var. 6537	Var. 6594	Var. 6651	Var. 6708	Var. 6765	Var. 6822
	2.5-10	Var. 6481	Var. 6538	Var. 6595	Var. 6652	Var. 6709	Var. 6766	Var. 6823
	2.5-5	Var. 6482	Var. 6539	Var. 6596	Var. 6653	Var. 6710	Var. 6767	Var. 6824
	5-200	Var. 6483	Var. 6540	Var. 6597	Var. 6654	Var. 6711	Var. 6768	Var. 6825
	5-175	Var. 6484	Var. 6541	Var. 6598	Var. 6655	Var. 6712	Var. 6769	Var. 6826
	5-150	Var. 6485	Var. 6542	Var. 6599	Var. 6656	Var. 6713	Var. 6770	Var. 6827
	5-125	Var. 6486	Var. 6543	Var. 6600	Var. 6657	Var. 6714	Var. 6771	Var. 6828
	5-100	Var. 6487	Var. 6544	Var. 6601	Var. 6658	Var. 6715	Var. 6772	Var. 6829
	5-75	Var. 6488	Var. 6545	Var. 6602	Var. 6659	Var. 6716	Var. 6773	Var. 6830
	5-50	Var. 6489	Var. 6546	Var. 6603	Var. 6660	Var. 6717	Var. 6774	Var. 6831
	5-25	Var. 6490	Var. 6547	Var. 6604	Var. 6661	Var. 6718	Var. 6775	Var. 6832
	5-10	Var. 6491	Var. 6548	Var. 6605	Var. 6662	Var. 6719	Var. 6776	Var. 6833
	10-200	Var. 6492	Var. 6549	Var. 6606	Var. 6663	Var. 6720	Var. 6777	Var. 6834
	10-150	Var. 6493	Var. 6550	Var. 6607	Var. 6664	Var. 6721	Var. 6778	Var. 6835
	10-100	Var. 6494	Var. 6551	Var. 6608	Var. 6665	Var. 6722	Var. 6779	Var. 6836
	10-75	Var. 6495	Var. 6552	Var. 6609	Var. 6666	Var. 6723	Var. 6780	Var. 6837
	10-50	Var. 6496	Var. 6553	Var. 6610	Var. 6667	Var. 6724	Var. 6781	Var. 6838
	10-25	Var. 6497	Var. 6554	Var. 6611	Var. 6668	Var. 6725	Var. 6782	Var. 6839
	25-200	Var. 6498	Var. 6555	Var. 6612	Var. 6669	Var. 6726	Var. 6783	Var. 6840
	25-150	Var. 6499	Var. 6556	Var. 6613	Var. 6670	Var. 6727	Var. 6784	Var. 6841
	25-100	Var. 6500	Var. 6557	Var. 6614	Var. 6671	Var. 6728	Var. 6785	Var. 6842
	25-75	Var. 6501	Var. 6558	Var. 6615	Var. 6672	Var. 6729	Var. 6786	Var. 6843
	25-50	Var. 6502	Var. 6559	Var. 6616	Var. 6673	Var. 6730	Var. 6787	Var. 6844
	50-200	Var. 6503	Var. 6560	Var. 6617	Var. 6674	Var. 6731	Var. 6788	Var. 6845
	50-150	Var. 6504	Var. 6561	Var. 6618	Var. 6675	Var. 6732	Var. 6789	Var. 6846
	50-100	Var. 6505	Var. 6562	Var. 6619	Var. 6676	Var. 6733	Var. 6790	Var. 6847
	50-75	Var. 6506	Var. 6563	Var. 6620	Var. 6677	Var. 6734	Var. 6791	Var. 6848
	75-200	Var. 6507	Var. 6564	Var. 6621	Var. 6678	Var. 6735	Var. 6792	Var. 6849

TABLE 24-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours)								
	4-6 hr	4-5 hr	5-8 hr	5-7 hr	5-6 hr	6-8 hr	6-7 hr	
75-175	Var. 6508	Var. 6565	Var. 6622	Var. 6679	Var. 6736	Var. 6793	Var. 6850	
75-150	Var. 6509	Var. 6566	Var. 6623	Var. 6680	Var. 6737	Var. 6794	Var. 6851	
75-125	Var. 6510	Var. 6567	Var. 6624	Var. 6681	Var. 6738	Var. 6795	Var. 6852	
75-100	Var. 6511	Var. 6568	Var. 6625	Var. 6682	Var. 6739	Var. 6796	Var. 6853	
100-200	Var. 6512	Var. 6569	Var. 6626	Var. 6683	Var. 6740	Var. 6797	Var. 6854	
100-175	Var. 6513	Var. 6570	Var. 6627	Var. 6684	Var. 6741	Var. 6798	Var. 6855	
100-150	Var. 6514	Var. 6571	Var. 6628	Var. 6685	Var. 6742	Var. 6799	Var. 6856	
100-125	Var. 6515	Var. 6572	Var. 6629	Var. 6686	Var. 6743	Var. 6800	Var. 6857	
125-200	Var. 6516	Var. 6573	Var. 6630	Var. 6687	Var. 6744	Var. 6801	Var. 6858	
125-175	Var. 6517	Var. 6574	Var. 6631	Var. 6688	Var. 6745	Var. 6802	Var. 6859	
125-150	Var. 6518	Var. 6575	Var. 6632	Var. 6689	Var. 6746	Var. 6803	Var. 6860	
150-200	Var. 6519	Var. 6576	Var. 6633	Var. 6690	Var. 6747	Var. 6804	Var. 6861	
150-200	Var. 6520	Var. 6577	Var. 6634	Var. 6691	Var. 6748	Var. 6805	Var. 6862	
175-200	Var. 6521	Var. 6578	Var. 6635	Var. 6692	Var. 6749	Var. 6806	Var. 6863	

Var. = Variation

TABLE 25

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours/Percent)								
	7-8 hr	at least 10%	at least 20%	at least 30%	at least 40%	at least 50%	10-50%	
Dosage	0.5-200	Var. 6864	Var. 6921	Var. 6978	Var. 7035	Var. 7092	Var. 7149	Var. 7206
(IU/kg rVWF:RCo activity)	0.5-150	Var. 6865	Var. 6922	Var. 6979	Var. 7036	Var. 7093	Var. 7150	Var. 7207
	0.5-100	Var. 6866	Var. 6923	Var. 6980	Var. 7037	Var. 7094	Var. 7151	Var. 7208
	0.5-75	Var. 6867	Var. 6924	Var. 6981	Var. 7038	Var. 7095	Var. 7152	Var. 7209
	0.5-50	Var. 6868	Var. 6925	Var. 6982	Var. 7039	Var. 7096	Var. 7153	Var. 7210
	0.5-25	Var. 6869	Var. 6926	Var. 6983	Var. 7040	Var. 7097	Var. 7154	Var. 7211
	0.5-10	Var. 6870	Var. 6927	Var. 6984	Var. 7041	Var. 7098	Var. 7155	Var. 7212
	0.5-5	Var. 6871	Var. 6928	Var. 6985	Var. 7042	Var. 7099	Var. 7156	Var. 7213
	0.5-2.5	Var. 6872	Var. 6929	Var. 6986	Var. 7043	Var. 7100	Var. 7157	Var. 7214
	0.5-1	Var. 6873	Var. 6930	Var. 6987	Var. 7044	Var. 7101	Var. 7158	Var. 7215
	2.5-200	Var. 6874	Var. 6931	Var. 6988	Var. 7045	Var. 7102	Var. 7159	Var. 7216
	2.5-150	Var. 6875	Var. 6932	Var. 6989	Var. 7046	Var. 7103	Var. 7160	Var. 7217
	2.5-100	Var. 6876	Var. 6933	Var. 6990	Var. 7047	Var. 7104	Var. 7161	Var. 7218
	2.5-75	Var. 6877	Var. 6934	Var. 6991	Var. 7048	Var. 7105	Var. 7162	Var. 7219
	2.5-50	Var. 6878	Var. 6935	Var. 6992	Var. 7049	Var. 7106	Var. 7163	Var. 7220
	2.5-25	Var. 6879	Var. 6936	Var. 6993	Var. 7050	Var. 7107	Var. 7164	Var. 7221
	2.5-10	Var. 6880	Var. 6937	Var. 6994	Var. 7051	Var. 7108	Var. 7165	Var. 7222
	2.5-5	Var. 6881	Var. 6938	Var. 6995	Var. 7052	Var. 7109	Var. 7166	Var. 7223
	5-200	Var. 6882	Var. 6939	Var. 6996	Var. 7053	Var. 7110	Var. 7167	Var. 7224
	5-175	Var. 6883	Var. 6940	Var. 6997	Var. 7054	Var. 7111	Var. 7168	Var. 7225
	5-150	Var. 6884	Var. 6941	Var. 6998	Var. 7055	Var. 7112	Var. 7169	Var. 7226
	5-125	Var. 6885	Var. 6942	Var. 6999	Var. 7056	Var. 7113	Var. 7170	Var. 7227
	5-100	Var. 6886	Var. 6943	Var. 7000	Var. 7057	Var. 7114	Var. 7171	Var. 7228
	5-75	Var. 6887	Var. 6944	Var. 7001	Var. 7058	Var. 7115	Var. 7172	Var. 7229
	5-50	Var. 6888	Var. 6945	Var. 7002	Var. 7059	Var. 7116	Var. 7173	Var. 7230
	5-25	Var. 6889	Var. 6946	Var. 7003	Var. 7060	Var. 7117	Var. 7174	Var. 7231
	5-10	Var. 6890	Var. 6947	Var. 7004	Var. 7061	Var. 7118	Var. 7175	Var. 7232
	10-200	Var. 6891	Var. 6948	Var. 7005	Var. 7062	Var. 7119	Var. 7176	Var. 7233
	10-150	Var. 6892	Var. 6949	Var. 7006	Var. 7063	Var. 7120	Var. 7177	Var. 7234
	10-100	Var. 6893	Var. 6950	Var. 7007	Var. 7064	Var. 7121	Var. 7178	Var. 7235
	10-75	Var. 6894	Var. 6951	Var. 7008	Var. 7065	Var. 7122	Var. 7179	Var. 7236
	10-50	Var. 6895	Var. 6952	Var. 7009	Var. 7066	Var. 7123	Var. 7180	Var. 7237
	10-25	Var. 6896	Var. 6953	Var. 7010	Var. 7067	Var. 7124	Var. 7181	Var. 7238
	25-200	Var. 6897	Var. 6954	Var. 7011	Var. 7068	Var. 7125	Var. 7182	Var. 7239
	25-150	Var. 6898	Var. 6955	Var. 7012	Var. 7069	Var. 7126	Var. 7183	Var. 7240
	25-100	Var. 6899	Var. 6956	Var. 7013	Var. 7070	Var. 7127	Var. 7184	Var. 7241
	25-75	Var. 6900	Var. 6957	Var. 7014	Var. 7071	Var. 7128	Var. 7185	Var. 7242
	25-50	Var. 6901	Var. 6958	Var. 7015	Var. 7072	Var. 7129	Var. 7186	Var. 7243
	50-200	Var. 6902	Var. 6959	Var. 7016	Var. 7073	Var. 7130	Var. 7187	Var. 7244
	50-150	Var. 6903	Var. 6960	Var. 7017	Var. 7074	Var. 7131	Var. 7188	Var. 7245
	50-100	Var. 6904	Var. 6961	Var. 7018	Var. 7075	Var. 7132	Var. 7189	Var. 7246
	50-75	Var. 6905	Var. 6962	Var. 7019	Var. 7076	Var. 7133	Var. 7190	Var. 7247
	75-200	Var. 6906	Var. 6963	Var. 7020	Var. 7077	Var. 7134	Var. 7191	Var. 7248
	75-175	Var. 6907	Var. 6964	Var. 7021	Var. 7078	Var. 7135	Var. 7192	Var. 7249

TABLE 25-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Hours/Percent)								
	7-8 hr	at least 10%	at least 20%	at least 30%	at least 40%	at least 50%	10-50%	
75-150	Var. 6908	Var. 6965	Var. 7022	Var. 7079	Var. 7136	Var. 7193	Var. 7250	
75-125	Var. 6909	Var. 6966	Var. 7023	Var. 7080	Var. 7137	Var. 7194	Var. 7251	
75-100	Var. 6910	Var. 6967	Var. 7024	Var. 7081	Var. 7138	Var. 7195	Var. 7252	
100-200	Var. 6911	Var. 6968	Var. 7025	Var. 7082	Var. 7139	Var. 7196	Var. 7253	
100-175	Var. 6912	Var. 6969	Var. 7026	Var. 7083	Var. 7140	Var. 7197	Var. 7254	
100-150	Var. 6913	Var. 6970	Var. 7027	Var. 7084	Var. 7141	Var. 7198	Var. 7255	
100-125	Var. 6914	Var. 6971	Var. 7028	Var. 7085	Var. 7142	Var. 7199	Var. 7256	
125-200	Var. 6915	Var. 6972	Var. 7029	Var. 7086	Var. 7143	Var. 7200	Var. 7257	
125-175	Var. 6916	Var. 6973	Var. 7030	Var. 7087	Var. 7144	Var. 7201	Var. 7258	
125-150	Var. 6917	Var. 6974	Var. 7031	Var. 7088	Var. 7145	Var. 7202	Var. 7259	
150-200	Var. 6918	Var. 6975	Var. 7032	Var. 7089	Var. 7146	Var. 7203	Var. 7260	
150-200	Var. 6919	Var. 6976	Var. 7033	Var. 7090	Var. 7147	Var. 7204	Var. 7261	
175-200	Var. 6920	Var. 6977	Var. 7034	Var. 7091	Var. 7148	Var. 7205	Var. 7262	

Var. = Variation

TABLE 26

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Percent)								
	10-40%	10-30%	10-20%	15-50%	15-40%	15-30%	15-20%	
Dosage	0.5-200	Var. 7263	Var. 7320	Var. 7377	Var. 7434	Var. 7491	Var. 7548	Var. 7605
(IU/kg rVWF:RCo	0.5-150	Var. 7264	Var. 7321	Var. 7378	Var. 7435	Var. 7492	Var. 7549	Var. 7606
activity)	0.5-100	Var. 7265	Var. 7322	Var. 7379	Var. 7436	Var. 7493	Var. 7550	Var. 7607
	0.5-75	Var. 7266	Var. 7323	Var. 7380	Var. 7437	Var. 7494	Var. 7551	Var. 7608
	0.5-50	Var. 7267	Var. 7324	Var. 7381	Var. 7438	Var. 7495	Var. 7552	Var. 7609
	0.5-25	Var. 7268	Var. 7325	Var. 7382	Var. 7439	Var. 7496	Var. 7553	Var. 7610
	0.5-10	Var. 7269	Var. 7326	Var. 7383	Var. 7440	Var. 7497	Var. 7554	Var. 7611
	0.5-5	Var. 7270	Var. 7327	Var. 7384	Var. 7441	Var. 7498	Var. 7555	Var. 7612
	0.5-2.5	Var. 7271	Var. 7328	Var. 7385	Var. 7442	Var. 7499	Var. 7556	Var. 7613
	0.5-1	Var. 7272	Var. 7329	Var. 7386	Var. 7443	Var. 7500	Var. 7557	Var. 7614
	2.5-200	Var. 7273	Var. 7330	Var. 7387	Var. 7444	Var. 7501	Var. 7558	Var. 7615
	2.5-150	Var. 7274	Var. 7331	Var. 7388	Var. 7445	Var. 7502	Var. 7559	Var. 7616
	2.5-100	Var. 7275	Var. 7332	Var. 7389	Var. 7446	Var. 7503	Var. 7560	Var. 7617
	2.5-75	Var. 7276	Var. 7333	Var. 7390	Var. 7447	Var. 7504	Var. 7561	Var. 7618
	2.5-50	Var. 7277	Var. 7334	Var. 7391	Var. 7448	Var. 7505	Var. 7562	Var. 7619
	2.5-25	Var. 7278	Var. 7335	Var. 7392	Var. 7449	Var. 7506	Var. 7563	Var. 7620
	2.5-10	Var. 7279	Var. 7336	Var. 7393	Var. 7450	Var. 7507	Var. 7564	Var. 7621
	2.5-5	Var. 7280	Var. 7337	Var. 7394	Var. 7451	Var. 7508	Var. 7565	Var. 7622
	5-200	Var. 7281	Var. 7338	Var. 7395	Var. 7452	Var. 7509	Var. 7566	Var. 7623
	5-175	Var. 7282	Var. 7339	Var. 7396	Var. 7453	Var. 7510	Var. 7567	Var. 7624
	5-150	Var. 7283	Var. 7340	Var. 7397	Var. 7454	Var. 7511	Var. 7568	Var. 7625
	5-125	Var. 7284	Var. 7341	Var. 7398	Var. 7455	Var. 7512	Var. 7569	Var. 7626
	5-100	Var. 7285	Var. 7342	Var. 7399	Var. 7456	Var. 7513	Var. 7570	Var. 7627
	5-75	Var. 7286	Var. 7343	Var. 7400	Var. 7457	Var. 7514	Var. 7571	Var. 7628
	5-50	Var. 7287	Var. 7344	Var. 7401	Var. 7458	Var. 7515	Var. 7572	Var. 7629
	5-25	Var. 7288	Var. 7345	Var. 7402	Var. 7459	Var. 7516	Var. 7573	Var. 7630
	5-10	Var. 7289	Var. 7346	Var. 7403	Var. 7460	Var. 7517	Var. 7574	Var. 7631
	10-200	Var. 7290	Var. 7347	Var. 7404	Var. 7461	Var. 7518	Var. 7575	Var. 7632
	10-150	Var. 7291	Var. 7348	Var. 7405	Var. 7462	Var. 7519	Var. 7576	Var. 7633
	10-100	Var. 7292	Var. 7349	Var. 7406	Var. 7463	Var. 7520	Var. 7577	Var. 7634
	10-75	Var. 7293	Var. 7350	Var. 7407	Var. 7464	Var. 7521	Var. 7578	Var. 7635
	10-50	Var. 7294	Var. 7351	Var. 7408	Var. 7465	Var. 7522	Var. 7579	Var. 7636
	10-25	Var. 7295	Var. 7352	Var. 7409	Var. 7466	Var. 7523	Var. 7580	Var. 7637
	25-200	Var. 7296	Var. 7353	Var. 7410	Var. 7467	Var. 7524	Var. 7581	Var. 7638
	25-150	Var. 7297	Var. 7354	Var. 7411	Var. 7468	Var. 7525	Var. 7582	Var. 7639
	25-100	Var. 7298	Var. 7355	Var. 7412	Var. 7469	Var. 7526	Var. 7583	Var. 7640
	25-75	Var. 7299	Var. 7356	Var. 7413	Var. 7470	Var. 7527	Var. 7584	Var. 7641
	25-50	Var. 7300	Var. 7357	Var. 7414	Var. 7471	Var. 7528	Var. 7585	Var. 7642
	50-200	Var. 7301	Var. 7358	Var. 7415	Var. 7472	Var. 7529	Var. 7586	Var. 7643
	50-150	Var. 7302	Var. 7359	Var. 7416	Var. 7473	Var. 7530	Var. 7587	Var. 7644
	50-100	Var. 7303	Var. 7360	Var. 7417	Var. 7474	Var. 7531	Var. 7588	Var. 7645
	50-75	Var. 7304	Var. 7361	Var. 7418	Var. 7475	Var. 7532	Var. 7589	Var. 7646
	75-200	Var. 7305	Var. 7362	Var. 7419	Var. 7476	Var. 7533	Var. 7590	Var. 7647
	75-175	Var. 7306	Var. 7363	Var. 7420	Var. 7477	Var. 7534	Var. 7591	Var. 7648
	75-150	Var. 7307	Var. 7364	Var. 7421	Var. 7478	Var. 7535	Var. 7592	Var. 7649

TABLE 26-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.								
Increased Stability (Percent)								
	10-40%	10-30%	10-20%	15-50%	15-40%	15-30%	15-20%	
75-125	Var. 7308	Var. 7365	Var. 7422	Var. 7479	Var. 7536	Var. 7593	Var. 7650	
75-100	Var. 7309	Var. 7366	Var. 7423	Var. 7480	Var. 7537	Var. 7594	Var. 7651	
100-200	Var. 7310	Var. 7367	Var. 7424	Var. 7481	Var. 7538	Var. 7595	Var. 7652	
100-175	Var. 7311	Var. 7368	Var. 7425	Var. 7482	Var. 7539	Var. 7596	Var. 7653	
100-150	Var. 7312	Var. 7369	Var. 7426	Var. 7483	Var. 7540	Var. 7597	Var. 7654	
100-125	Var. 7313	Var. 7370	Var. 7427	Var. 7484	Var. 7541	Var. 7598	Var. 7655	
125-200	Var. 7314	Var. 7371	Var. 7428	Var. 7485	Var. 7542	Var. 7599	Var. 7656	
125-175	Var. 7315	Var. 7372	Var. 7429	Var. 7486	Var. 7543	Var. 7600	Var. 7657	
125-150	Var. 7316	Var. 7373	Var. 7430	Var. 7487	Var. 7544	Var. 7601	Var. 7658	
150-200	Var. 7317	Var. 7374	Var. 7431	Var. 7488	Var. 7545	Var. 7602	Var. 7659	
150-200	Var. 7318	Var. 7375	Var. 7432	Var. 7489	Var. 7546	Var. 7603	Var. 7660	
175-200	Var. 7319	Var. 7376	Var. 7433	Var. 7490	Var. 7547	Var. 7604	Var. 7661	

Var. = Variation

TABLE 27

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Percent)							
	20-50%	20-40%	20-30%	30-50%	30-40%	40-50%	
Dosage	0.5-200	Var. 7662	Var. 7719	Var. 7776	Var. 7833	Var. 7890	Var. 7947
(IU/kg rVWF:RCo	0.5-150	Var. 7663	Var. 7720	Var. 7777	Var. 7834	Var. 7891	Var. 7948
activity)	0.5-100	Var. 7664	Var. 7721	Var. 7778	Var. 7835	Var. 7892	Var. 7949
	0.5-75	Var. 7665	Var. 7722	Var. 7779	Var. 7836	Var. 7893	Var. 7950
	0.5-50	Var. 7666	Var. 7723	Var. 7780	Var. 7837	Var. 7894	Var. 7951
	0.5-25	Var. 7667	Var. 7724	Var. 7781	Var. 7838	Var. 7895	Var. 7952
	0.5-10	Var. 7668	Var. 7725	Var. 7782	Var. 7839	Var. 7896	Var. 7953
	0.5-5	Var. 7669	Var. 7726	Var. 7783	Var. 7840	Var. 7897	Var. 7954
	0.5-2.5	Var. 7670	Var. 7727	Var. 7784	Var. 7841	Var. 7898	Var. 7955
	0.5-1	Var. 7671	Var. 7728	Var. 7785	Var. 7842	Var. 7899	Var. 7956
	2.5-200	Var. 7672	Var. 7729	Var. 7786	Var. 7843	Var. 7900	Var. 7957
	2.5-150	Var. 7673	Var. 7730	Var. 7787	Var. 7844	Var. 7901	Var. 7958
	2.5-100	Var. 7674	Var. 7731	Var. 7788	Var. 7845	Var. 7902	Var. 7959
	2.5-75	Var. 7675	Var. 7732	Var. 7789	Var. 7846	Var. 7903	Var. 7960
	2.5-50	Var. 7676	Var. 7733	Var. 7790	Var. 7847	Var. 7904	Var. 7961
	2.5-25	Var. 7677	Var. 7734	Var. 7791	Var. 7848	Var. 7905	Var. 7962
	2.5-10	Var. 7678	Var. 7735	Var. 7792	Var. 7849	Var. 7906	Var. 7963
	2.5-5	Var. 7679	Var. 7736	Var. 7793	Var. 7850	Var. 7907	Var. 7964
	5-200	Var. 7680	Var. 7737	Var. 7794	Var. 7851	Var. 7908	Var. 7965
	5-175	Var. 7681	Var. 7738	Var. 7795	Var. 7852	Var. 7909	Var. 7966
	5-150	Var. 7682	Var. 7739	Var. 7796	Var. 7853	Var. 7910	Var. 7967
	5-125	Var. 7683	Var. 7740	Var. 7797	Var. 7854	Var. 7911	Var. 7968
	5-100	Var. 7684	Var. 7741	Var. 7798	Var. 7855	Var. 7912	Var. 7969
	5-75	Var. 7685	Var. 7742	Var. 7799	Var. 7856	Var. 7913	Var. 7970
	5-50	Var. 7686	Var. 7743	Var. 7800	Var. 7857	Var. 7914	Var. 7971
	5-25	Var. 7687	Var. 7744	Var. 7801	Var. 7858	Var. 7915	Var. 7972
	5-10	Var. 7688	Var. 7745	Var. 7802	Var. 7859	Var. 7916	Var. 7973
	10-200	Var. 7689	Var. 7746	Var. 7803	Var. 7860	Var. 7917	Var. 7974
	10-150	Var. 7690	Var. 7747	Var. 7804	Var. 7861	Var. 7918	Var. 7975
	10-100	Var. 7691	Var. 7748	Var. 7805	Var. 7862	Var. 7919	Var. 7976
	10-75	Var. 7692	Var. 7749	Var. 7806	Var. 7863	Var. 7920	Var. 7977
	10-50	Var. 7693	Var. 7750	Var. 7807	Var. 7864	Var. 7921	Var. 7978
	10-25	Var. 7694	Var. 7751	Var. 7808	Var. 7865	Var. 7922	Var. 7979
	25-200	Var. 7695	Var. 7752	Var. 7809	Var. 7866	Var. 7923	Var. 7980
	25-150	Var. 7696	Var. 7753	Var. 7810	Var. 7867	Var. 7924	Var. 7981
	25-100	Var. 7697	Var. 7754	Var. 7811	Var. 7868	Var. 7925	Var. 7982
	25-75	Var. 7698	Var. 7755	Var. 7812	Var. 7869	Var. 7926	Var. 7983
	25-50	Var. 7699	Var. 7756	Var. 7813	Var. 7870	Var. 7927	Var. 7984
	50-200	Var. 7700	Var. 7757	Var. 7814	Var. 7871	Var. 7928	Var. 7985
	50-150	Var. 7701	Var. 7758	Var. 7815	Var. 7872	Var. 7929	Var. 7986
	50-100	Var. 7702	Var. 7759	Var. 7816	Var. 7873	Var. 7930	Var. 7987
	50-75	Var. 7703	Var. 7760	Var. 7817	Var. 7874	Var. 7931	Var. 7988
	75-200	Var. 7704	Var. 7761	Var. 7818	Var. 7875	Var. 7932	Var. 7989
	75-175	Var. 7705	Var. 7762	Var. 7819	Var. 7876	Var. 7933	Var. 7990
	75-150	Var. 7706	Var. 7763	Var. 7820	Var. 7877	Var. 7934	Var. 7991
	75-125	Var. 7707	Var. 7764	Var. 7821	Var. 7878	Var. 7935	Var. 7992
	75-100	Var. 7708	Var. 7765	Var. 7822	Var. 7879	Var. 7936	Var. 7993

TABLE 27-continued

Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.							
Increased Stability (Percent)							
	20-50%	20-40%	20-30%	30-50%	30-40%	40-50%	
100-200	Var. 7709	Var. 7766	Var. 7823	Var. 7880	Var. 7937	Var. 7994	
100-175	Var. 7710	Var. 7767	Var. 7824	Var. 7881	Var. 7938	Var. 7995	
100-150	Var. 7711	Var. 7768	Var. 7825	Var. 7882	Var. 7939	Var. 7996	
100-125	Var. 7712	Var. 7769	Var. 7826	Var. 7883	Var. 7940	Var. 7997	
125-200	Var. 7713	Var. 7770	Var. 7827	Var. 7884	Var. 7941	Var. 7998	
125-175	Var. 7714	Var. 7771	Var. 7828	Var. 7885	Var. 7942	Var. 7999	
125-150	Var. 7715	Var. 7772	Var. 7829	Var. 7886	Var. 7943	Var. 8000	
150-200	Var. 7716	Var. 7773	Var. 7830	Var. 7887	Var. 7944	Var. 8001	
150-200	Var. 7717	Var. 7774	Var. 7831	Var. 7888	Var. 7945	Var. 8002	
175-200	Var. 7718	Var. 7775	Var. 7832	Var. 7889	Var. 7946	Var. 8003	

Var. = Variation

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of

FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of from 40 mU/ μ g to 60 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of at least 60 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the

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method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of at least 80 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity selected from variations 1 to 133 found in Table 1, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF administered to the

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subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

TABLE 28

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
		Specific Activity (mU/ μ g)						
		at least 20	at least 30	at least 40	at least 50	at least 60	at least 70	at least 80
Dosage (IU/kg rVWF:RCo activity)	0.5-200	Var. 8004	Var. 8061	Var. 8118	Var. 8175	Var. 8232	Var. 8289	Var. 8346
	0.5-150	Var. 8005	Var. 8062	Var. 8119	Var. 8176	Var. 8233	Var. 8290	Var. 8347
	0.5-100	Var. 8006	Var. 8063	Var. 8120	Var. 8177	Var. 8234	Var. 8291	Var. 8348
	0.5-75	Var. 8007	Var. 8064	Var. 8121	Var. 8178	Var. 8235	Var. 8292	Var. 8349
	0.5-50	Var. 8008	Var. 8065	Var. 8122	Var. 8179	Var. 8236	Var. 8293	Var. 8350
	0.5-25	Var. 8009	Var. 8066	Var. 8123	Var. 8180	Var. 8237	Var. 8294	Var. 8351
	0.5-10	Var. 8010	Var. 8067	Var. 8124	Var. 8181	Var. 8238	Var. 8295	Var. 8352
	0.5-5	Var. 8011	Var. 8068	Var. 8125	Var. 8182	Var. 8239	Var. 8296	Var. 8353
	0.5-2.5	Var. 8012	Var. 8069	Var. 8126	Var. 8183	Var. 8240	Var. 8297	Var. 8354
	0.5-1	Var. 8013	Var. 8070	Var. 8127	Var. 8184	Var. 8241	Var. 8298	Var. 8355
	2.5-200	Var. 8014	Var. 8071	Var. 8128	Var. 8185	Var. 8242	Var. 8299	Var. 8356
	2.5-150	Var. 8015	Var. 8072	Var. 8129	Var. 8186	Var. 8243	Var. 8300	Var. 8357
	2.5-100	Var. 8016	Var. 8073	Var. 8130	Var. 8187	Var. 8244	Var. 8301	Var. 8358
	2.5-75	Var. 8017	Var. 8074	Var. 8131	Var. 8188	Var. 8245	Var. 8302	Var. 8359
	2.5-50	Var. 8018	Var. 8075	Var. 8132	Var. 8189	Var. 8246	Var. 8303	Var. 8360
	2.5-25	Var. 8019	Var. 8076	Var. 8133	Var. 8190	Var. 8247	Var. 8304	Var. 8361
	2.5-10	Var. 8020	Var. 8077	Var. 8134	Var. 8191	Var. 8248	Var. 8305	Var. 8362
	2.5-5	Var. 8021	Var. 8078	Var. 8135	Var. 8192	Var. 8249	Var. 8306	Var. 8363
	5-200	Var. 8022	Var. 8079	Var. 8136	Var. 8193	Var. 8250	Var. 8307	Var. 8364
	5-175	Var. 8023	Var. 8080	Var. 8137	Var. 8194	Var. 8251	Var. 8308	Var. 8365
	5-150	Var. 8024	Var. 8081	Var. 8138	Var. 8195	Var. 8252	Var. 8309	Var. 8366
	5-125	Var. 8025	Var. 8082	Var. 8139	Var. 8196	Var. 8253	Var. 8310	Var. 8367
	5-100	Var. 8026	Var. 8083	Var. 8140	Var. 8197	Var. 8254	Var. 8311	Var. 8368
	5-75	Var. 8027	Var. 8084	Var. 8141	Var. 8198	Var. 8255	Var. 8312	Var. 8369
	5-50	Var. 8028	Var. 8085	Var. 8142	Var. 8199	Var. 8256	Var. 8313	Var. 8370
	5-25	Var. 8029	Var. 8086	Var. 8143	Var. 8200	Var. 8257	Var. 8314	Var. 8371
	5-10	Var. 8030	Var. 8087	Var. 8144	Var. 8201	Var. 8258	Var. 8315	Var. 8372
	10-200	Var. 8031	Var. 8088	Var. 8145	Var. 8202	Var. 8259	Var. 8316	Var. 8373
	10-150	Var. 8032	Var. 8089	Var. 8146	Var. 8203	Var. 8260	Var. 8317	Var. 8374
	10-100	Var. 8033	Var. 8090	Var. 8147	Var. 8204	Var. 8261	Var. 8318	Var. 8375
	10-75	Var. 8034	Var. 8091	Var. 8148	Var. 8205	Var. 8262	Var. 8319	Var. 8376
	10-50	Var. 8035	Var. 8092	Var. 8149	Var. 8206	Var. 8263	Var. 8320	Var. 8377
	10-25	Var. 8036	Var. 8093	Var. 8150	Var. 8207	Var. 8264	Var. 8321	Var. 8378
	25-200	Var. 8037	Var. 8094	Var. 8151	Var. 8208	Var. 8265	Var. 8322	Var. 8379
	25-150	Var. 8038	Var. 8095	Var. 8152	Var. 8209	Var. 8266	Var. 8323	Var. 8380
	25-100	Var. 8039	Var. 8096	Var. 8153	Var. 8210	Var. 8267	Var. 8324	Var. 8381
	25-75	Var. 8040	Var. 8097	Var. 8154	Var. 8211	Var. 8268	Var. 8325	Var. 8382
	25-50	Var. 8041	Var. 8098	Var. 8155	Var. 8212	Var. 8269	Var. 8326	Var. 8383
	50-200	Var. 8042	Var. 8099	Var. 8156	Var. 8213	Var. 8270	Var. 8327	Var. 8384
	50-150	Var. 8043	Var. 8100	Var. 8157	Var. 8214	Var. 8271	Var. 8328	Var. 8385
	50-100	Var. 8044	Var. 8101	Var. 8158	Var. 8215	Var. 8272	Var. 8329	Var. 8386

TABLE 28-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	at least 20	at least 30	at least 40	at least 50	at least 60	at least 70	at least 80	
50-75	Var. 8045	Var. 8102	Var. 8159	Var. 8216	Var. 8273	Var. 8330	Var. 8387	
75-200	Var. 8046	Var. 8103	Var. 8160	Var. 8217	Var. 8274	Var. 8331	Var. 8388	
75-175	Var. 8047	Var. 8104	Var. 8161	Var. 8218	Var. 8275	Var. 8332	Var. 8389	
75-150	Var. 8048	Var. 8105	Var. 8162	Var. 8219	Var. 8276	Var. 8333	Var. 8390	
75-125	Var. 8049	Var. 8106	Var. 8163	Var. 8220	Var. 8277	Var. 8334	Var. 8391	
75-100	Var. 8050	Var. 8107	Var. 8164	Var. 8221	Var. 8278	Var. 8335	Var. 8392	
100-200	Var. 8051	Var. 8108	Var. 8165	Var. 8222	Var. 8279	Var. 8336	Var. 8393	
100-175	Var. 8052	Var. 8109	Var. 8166	Var. 8223	Var. 8280	Var. 8337	Var. 8394	
100-150	Var. 8053	Var. 8110	Var. 8167	Var. 8224	Var. 8281	Var. 8338	Var. 8395	
100-125	Var. 8054	Var. 8111	Var. 8168	Var. 8225	Var. 8282	Var. 8339	Var. 8396	
125-200	Var. 8055	Var. 8112	Var. 8169	Var. 8226	Var. 8283	Var. 8340	Var. 8397	
125-175	Var. 8056	Var. 8113	Var. 8170	Var. 8227	Var. 8284	Var. 8341	Var. 8398	
125-150	Var. 8057	Var. 8114	Var. 8171	Var. 8228	Var. 8285	Var. 8342	Var. 8399	
150-200	Var. 8058	Var. 8115	Var. 8172	Var. 8229	Var. 8286	Var. 8343	Var. 8400	
150-200	Var. 8059	Var. 8116	Var. 8173	Var. 8230	Var. 8287	Var. 8344	Var. 8401	
175-200	Var. 8060	Var. 8117	Var. 8174	Var. 8231	Var. 8288	Var. 8345	Var. 8402	

Var. = Variation

TABLE 29

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	at least 90	at least 100	at least 125	at least 150	20-150	20-125	20-100	
Dosage	0.5-200	Var. 8403	Var. 8460	Var. 8517	Var. 8574	Var. 8631	Var. 8688	Var. 8745
(IU/kg rVWF:RCo	0.5-150	Var. 8404	Var. 8461	Var. 8518	Var. 8575	Var. 8632	Var. 8689	Var. 8746
activity)	0.5-100	Var. 8405	Var. 8462	Var. 8519	Var. 8576	Var. 8633	Var. 8690	Var. 8747
	0.5-75	Var. 8406	Var. 8463	Var. 8520	Var. 8577	Var. 8634	Var. 8691	Var. 8748
	0.5-50	Var. 8407	Var. 8464	Var. 8521	Var. 8578	Var. 8635	Var. 8692	Var. 8749
	0.5-25	Var. 8408	Var. 8465	Var. 8522	Var. 8579	Var. 8636	Var. 8693	Var. 8750
	0.5-10	Var. 8409	Var. 8466	Var. 8523	Var. 8580	Var. 8637	Var. 8694	Var. 8751
	0.5-5	Var. 8410	Var. 8467	Var. 8524	Var. 8581	Var. 8638	Var. 8695	Var. 8752
	0.5-2.5	Var. 8411	Var. 8468	Var. 8525	Var. 8582	Var. 8639	Var. 8696	Var. 8753
	0.5-1	Var. 8412	Var. 8469	Var. 8526	Var. 8583	Var. 8640	Var. 8697	Var. 8754
	2.5-200	Var. 8413	Var. 8470	Var. 8527	Var. 8584	Var. 8641	Var. 8698	Var. 8755
	2.5-150	Var. 8414	Var. 8471	Var. 8528	Var. 8585	Var. 8642	Var. 8699	Var. 8756
	2.5-100	Var. 8415	Var. 8472	Var. 8529	Var. 8586	Var. 8643	Var. 8700	Var. 8757
	2.5-75	Var. 8416	Var. 8473	Var. 8530	Var. 8587	Var. 8644	Var. 8701	Var. 8758
	2.5-50	Var. 8417	Var. 8474	Var. 8531	Var. 8588	Var. 8645	Var. 8702	Var. 8759
	2.5-25	Var. 8418	Var. 8475	Var. 8532	Var. 8589	Var. 8646	Var. 8703	Var. 8760
	2.5-10	Var. 8419	Var. 8476	Var. 8533	Var. 8590	Var. 8647	Var. 8704	Var. 8761
	2.5-5	Var. 8420	Var. 8477	Var. 8534	Var. 8591	Var. 8648	Var. 8705	Var. 8762
	5-200	Var. 8421	Var. 8478	Var. 8535	Var. 8592	Var. 8649	Var. 8706	Var. 8763
	5-175	Var. 8422	Var. 8479	Var. 8536	Var. 8593	Var. 8650	Var. 8707	Var. 8764
	5-150	Var. 8423	Var. 8480	Var. 8537	Var. 8594	Var. 8651	Var. 8708	Var. 8765
	5-125	Var. 8424	Var. 8481	Var. 8538	Var. 8595	Var. 8652	Var. 8709	Var. 8766
	5-100	Var. 8425	Var. 8482	Var. 8539	Var. 8596	Var. 8653	Var. 8710	Var. 8767
	5-75	Var. 8426	Var. 8483	Var. 8540	Var. 8597	Var. 8654	Var. 8711	Var. 8768
	5-50	Var. 8427	Var. 8484	Var. 8541	Var. 8598	Var. 8655	Var. 8712	Var. 8769
	5-25	Var. 8428	Var. 8485	Var. 8542	Var. 8599	Var. 8656	Var. 8713	Var. 8770
	5-10	Var. 8429	Var. 8486	Var. 8543	Var. 8600	Var. 8657	Var. 8714	Var. 8771
	10-200	Var. 8430	Var. 8487	Var. 8544	Var. 8601	Var. 8658	Var. 8715	Var. 8772
	10-150	Var. 8431	Var. 8488	Var. 8545	Var. 8602	Var. 8659	Var. 8716	Var. 8773
	10-100	Var. 8432	Var. 8489	Var. 8546	Var. 8603	Var. 8660	Var. 8717	Var. 8774
	10-75	Var. 8433	Var. 8490	Var. 8547	Var. 8604	Var. 8661	Var. 8718	Var. 8775
	10-50	Var. 8434	Var. 8491	Var. 8548	Var. 8605	Var. 8662	Var. 8719	Var. 8776
	10-25	Var. 8435	Var. 8492	Var. 8549	Var. 8606	Var. 8663	Var. 8720	Var. 8777
	25-200	Var. 8436	Var. 8493	Var. 8550	Var. 8607	Var. 8664	Var. 8721	Var. 8778
	25-150	Var. 8437	Var. 8494	Var. 8551	Var. 8608	Var. 8665	Var. 8722	Var. 8779
	25-100	Var. 8438	Var. 8495	Var. 8552	Var. 8609	Var. 8666	Var. 8723	Var. 8780
	25-75	Var. 8439	Var. 8496	Var. 8553	Var. 8610	Var. 8667	Var. 8724	Var. 8781
	25-50	Var. 8440	Var. 8497	Var. 8554	Var. 8611	Var. 8668	Var. 8725	Var. 8782
	50-200	Var. 8441	Var. 8498	Var. 8555	Var. 8612	Var. 8669	Var. 8726	Var. 8783
	50-150	Var. 8442	Var. 8499	Var. 8556	Var. 8613	Var. 8670	Var. 8727	Var. 8784
	50-100	Var. 8443	Var. 8500	Var. 8557	Var. 8614	Var. 8671	Var. 8728	Var. 8785
	50-75	Var. 8444	Var. 8501	Var. 8558	Var. 8615	Var. 8672	Var. 8729	Var. 8786
	75-200	Var. 8445	Var. 8502	Var. 8559	Var. 8616	Var. 8673	Var. 8730	Var. 8787

TABLE 29-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	at least 90	at least 100	at least 125	at least 150	20-150	20-125	20-100	
75-175	Var. 8446	Var. 8503	Var. 8560	Var. 8617	Var. 8674	Var. 8731	Var. 8788	
75-150	Var. 8447	Var. 8504	Var. 8561	Var. 8618	Var. 8675	Var. 8732	Var. 8789	
75-125	Var. 8448	Var. 8505	Var. 8562	Var. 8619	Var. 8676	Var. 8733	Var. 8790	
75-100	Var. 8449	Var. 8506	Var. 8563	Var. 8620	Var. 8677	Var. 8734	Var. 8791	
100-200	Var. 8450	Var. 8507	Var. 8564	Var. 8621	Var. 8678	Var. 8735	Var. 8792	
100-175	Var. 8451	Var. 8508	Var. 8565	Var. 8622	Var. 8679	Var. 8736	Var. 8793	
100-150	Var. 8452	Var. 8509	Var. 8566	Var. 8623	Var. 8680	Var. 8737	Var. 8794	
100-125	Var. 8453	Var. 8510	Var. 8567	Var. 8624	Var. 8681	Var. 8738	Var. 8795	
125-200	Var. 8454	Var. 8511	Var. 8568	Var. 8625	Var. 8682	Var. 8739	Var. 8796	
125-175	Var. 8455	Var. 8512	Var. 8569	Var. 8626	Var. 8683	Var. 8740	Var. 8797	
125-150	Var. 8456	Var. 8513	Var. 8570	Var. 8627	Var. 8684	Var. 8741	Var. 8798	
150-200	Var. 8457	Var. 8514	Var. 8571	Var. 8628	Var. 8685	Var. 8742	Var. 8799	
150-200	Var. 8458	Var. 8515	Var. 8572	Var. 8629	Var. 8686	Var. 8743	Var. 8800	
175-200	Var. 8459	Var. 8516	Var. 8573	Var. 8630	Var. 8687	Var. 8744	Var. 8801	

Var. = Variation

TABLE 30

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	20-90	20-80	20-70	20-60	20-50	20-40	40-150	
Dosage (IU/kg rVWF:RCo activity)	0.5-200	Var. 8802	Var. 8859	Var. 8916	Var. 8973	Var. 9030	Var. 9087	Var. 9144
	0.5-150	Var. 8803	Var. 8860	Var. 8917	Var. 8974	Var. 9031	Var. 9088	Var. 9145
	0.5-100	Var. 8804	Var. 8861	Var. 8918	Var. 8975	Var. 9032	Var. 9089	Var. 9146
	0.5-75	Var. 8805	Var. 8862	Var. 8919	Var. 8976	Var. 9033	Var. 9090	Var. 9147
	0.5-50	Var. 8806	Var. 8863	Var. 8920	Var. 8977	Var. 9034	Var. 9091	Var. 9148
	0.5-25	Var. 8807	Var. 8864	Var. 8921	Var. 8978	Var. 9035	Var. 9092	Var. 9149
	0.5-10	Var. 8808	Var. 8865	Var. 8922	Var. 8979	Var. 9036	Var. 9093	Var. 9150
	0.5-5	Var. 8809	Var. 8866	Var. 8923	Var. 8980	Var. 9037	Var. 9094	Var. 9151
	0.5-2.5	Var. 8810	Var. 8867	Var. 8924	Var. 8981	Var. 9038	Var. 9095	Var. 9152
	0.5-1	Var. 8811	Var. 8868	Var. 8925	Var. 8982	Var. 9039	Var. 9096	Var. 9153
	2.5-200	Var. 8812	Var. 8869	Var. 8926	Var. 8983	Var. 9040	Var. 9097	Var. 9154
	2.5-150	Var. 8813	Var. 8870	Var. 8927	Var. 8984	Var. 9041	Var. 9098	Var. 9155
	2.5-100	Var. 8814	Var. 8871	Var. 8928	Var. 8985	Var. 9042	Var. 9099	Var. 9156
	2.5-75	Var. 8815	Var. 8872	Var. 8929	Var. 8986	Var. 9043	Var. 9100	Var. 9157
	2.5-50	Var. 8816	Var. 8873	Var. 8930	Var. 8987	Var. 9044	Var. 9101	Var. 9158
	2.5-25	Var. 8817	Var. 8874	Var. 8931	Var. 8988	Var. 9045	Var. 9102	Var. 9159
	2.5-10	Var. 8818	Var. 8875	Var. 8932	Var. 8989	Var. 9046	Var. 9103	Var. 9160
	2.5-5	Var. 8819	Var. 8876	Var. 8933	Var. 8990	Var. 9047	Var. 9104	Var. 9161
	5-200	Var. 8820	Var. 8877	Var. 8934	Var. 8991	Var. 9048	Var. 9105	Var. 9162
	5-175	Var. 8821	Var. 8878	Var. 8935	Var. 8992	Var. 9049	Var. 9106	Var. 9163
	5-150	Var. 8822	Var. 8879	Var. 8936	Var. 8993	Var. 9050	Var. 9107	Var. 9164
	5-125	Var. 8823	Var. 8880	Var. 8937	Var. 8994	Var. 9051	Var. 9108	Var. 9165
	5-100	Var. 8824	Var. 8881	Var. 8938	Var. 8995	Var. 9052	Var. 9109	Var. 9166
	5-75	Var. 8825	Var. 8882	Var. 8939	Var. 8996	Var. 9053	Var. 9110	Var. 9167
	5-50	Var. 8826	Var. 8883	Var. 8940	Var. 8997	Var. 9054	Var. 9111	Var. 9168
	5-25	Var. 8827	Var. 8884	Var. 8941	Var. 8998	Var. 9055	Var. 9112	Var. 9169
	5-10	Var. 8828	Var. 8885	Var. 8942	Var. 8999	Var. 9056	Var. 9113	Var. 9170
	10-200	Var. 8829	Var. 8886	Var. 8943	Var. 9000	Var. 9057	Var. 9114	Var. 9171
	10-150	Var. 8830	Var. 8887	Var. 8944	Var. 9001	Var. 9058	Var. 9115	Var. 9172
	10-100	Var. 8831	Var. 8888	Var. 8945	Var. 9002	Var. 9059	Var. 9116	Var. 9173
	10-75	Var. 8832	Var. 8889	Var. 8946	Var. 9003	Var. 9060	Var. 9117	Var. 9174
	10-50	Var. 8833	Var. 8890	Var. 8947	Var. 9004	Var. 9061	Var. 9118	Var. 9175
	10-25	Var. 8834	Var. 8891	Var. 8948	Var. 9005	Var. 9062	Var. 9119	Var. 9176
	25-200	Var. 8835	Var. 8892	Var. 8949	Var. 9006	Var. 9063	Var. 9120	Var. 9177
	25-150	Var. 8836	Var. 8893	Var. 8950	Var. 9007	Var. 9064	Var. 9121	Var. 9178
	25-100	Var. 8837	Var. 8894	Var. 8951	Var. 9008	Var. 9065	Var. 9122	Var. 9179
	25-75	Var. 8838	Var. 8895	Var. 8952	Var. 9009	Var. 9066	Var. 9123	Var. 9180
	25-50	Var. 8839	Var. 8896	Var. 8953	Var. 9010	Var. 9067	Var. 9124	Var. 9181
	50-200	Var. 8840	Var. 8897	Var. 8954	Var. 9011	Var. 9068	Var. 9125	Var. 9182
	50-150	Var. 8841	Var. 8898	Var. 8955	Var. 9012	Var. 9069	Var. 9126	Var. 9183
	50-100	Var. 8842	Var. 8899	Var. 8956	Var. 9013	Var. 9070	Var. 9127	Var. 9184
	50-75	Var. 8843	Var. 8900	Var. 8957	Var. 9014	Var. 9071	Var. 9128	Var. 9185
	75-200	Var. 8844	Var. 8901	Var. 8958	Var. 9015	Var. 9072	Var. 9129	Var. 9186
	75-175	Var. 8845	Var. 8902	Var. 8959	Var. 9016	Var. 9073	Var. 9130	Var. 9187
	75-150	Var. 8846	Var. 8903	Var. 8960	Var. 9017	Var. 9074	Var. 9131	Var. 9188

TABLE 30-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	20-90	20-80	20-70	20-60	20-50	20-40	40-150	
75-125	Var. 8847	Var. 8904	Var. 8961	Var. 9018	Var. 9075	Var. 9132	Var. 9189	
75-100	Var. 8848	Var. 8905	Var. 8962	Var. 9019	Var. 9076	Var. 9133	Var. 9190	
100-200	Var. 8849	Var. 8906	Var. 8963	Var. 9020	Var. 9077	Var. 9134	Var. 9191	
100-175	Var. 8850	Var. 8907	Var. 8964	Var. 9021	Var. 9078	Var. 9135	Var. 9192	
100-150	Var. 8851	Var. 8908	Var. 8965	Var. 9022	Var. 9079	Var. 9136	Var. 9193	
100-125	Var. 8852	Var. 8909	Var. 8966	Var. 9023	Var. 9080	Var. 9137	Var. 9194	
125-200	Var. 8853	Var. 8910	Var. 8967	Var. 9024	Var. 9081	Var. 9138	Var. 9195	
125-175	Var. 8854	Var. 8911	Var. 8968	Var. 9025	Var. 9082	Var. 9139	Var. 9196	
125-150	Var. 8855	Var. 8912	Var. 8969	Var. 9026	Var. 9083	Var. 9140	Var. 9197	
150-200	Var. 8856	Var. 8913	Var. 8970	Var. 9027	Var. 9084	Var. 9141	Var. 9198	
150-200	Var. 8857	Var. 8914	Var. 8971	Var. 9028	Var. 9085	Var. 9142	Var. 9199	
175-200	Var. 8858	Var. 8915	Var. 8972	Var. 9029	Var. 9086	Var. 9143	Var. 9200	

Var. = Variation

TABLE 31

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	40-125	40-100	40-90	40-80	40-70	40-60	40-50	
Dosage	0.5-200	Var. 9201	Var. 9258	Var. 9315	Var. 9372	Var. 9429	Var. 9486	Var. 9543
(IU/kg rVWF:RCo	0.5-150	Var. 9202	Var. 9259	Var. 9316	Var. 9373	Var. 9430	Var. 9487	Var. 9544
activity)	0.5-100	Var. 9203	Var. 9260	Var. 9317	Var. 9374	Var. 9431	Var. 9488	Var. 9545
	0.5-75	Var. 9204	Var. 9261	Var. 9318	Var. 9375	Var. 9432	Var. 9489	Var. 9546
	0.5-50	Var. 9205	Var. 9262	Var. 9319	Var. 9376	Var. 9433	Var. 9490	Var. 9547
	0.5-25	Var. 9206	Var. 9263	Var. 9320	Var. 9377	Var. 9434	Var. 9491	Var. 9548
	0.5-10	Var. 9207	Var. 9264	Var. 9321	Var. 9378	Var. 9435	Var. 9492	Var. 9549
	0.5-5	Var. 9208	Var. 9265	Var. 9322	Var. 9379	Var. 9436	Var. 9493	Var. 9550
	0.5-2.5	Var. 9209	Var. 9266	Var. 9323	Var. 9380	Var. 9437	Var. 9494	Var. 9551
	0.5-1	Var. 9210	Var. 9267	Var. 9324	Var. 9381	Var. 9438	Var. 9495	Var. 9552
	2.5-200	Var. 9211	Var. 9268	Var. 9325	Var. 9382	Var. 9439	Var. 9496	Var. 9553
	2.5-150	Var. 9212	Var. 9269	Var. 9326	Var. 9383	Var. 9440	Var. 9497	Var. 9554
	2.5-100	Var. 9213	Var. 9270	Var. 9327	Var. 9384	Var. 9441	Var. 9498	Var. 9555
	2.5-75	Var. 9214	Var. 9271	Var. 9328	Var. 9385	Var. 9442	Var. 9499	Var. 9556
	2.5-50	Var. 9215	Var. 9272	Var. 9329	Var. 9386	Var. 9443	Var. 9500	Var. 9557
	2.5-25	Var. 9216	Var. 9273	Var. 9330	Var. 9387	Var. 9444	Var. 9501	Var. 9558
	2.5-10	Var. 9217	Var. 9274	Var. 9331	Var. 9388	Var. 9445	Var. 9502	Var. 9559
	2.5-5	Var. 9218	Var. 9275	Var. 9332	Var. 9389	Var. 9446	Var. 9503	Var. 9560
	5-200	Var. 9219	Var. 9276	Var. 9333	Var. 9390	Var. 9447	Var. 9504	Var. 9561
	5-175	Var. 9220	Var. 9277	Var. 9334	Var. 9391	Var. 9448	Var. 9505	Var. 9562
	5-150	Var. 9221	Var. 9278	Var. 9335	Var. 9392	Var. 9449	Var. 9506	Var. 9563
	5-125	Var. 9222	Var. 9279	Var. 9336	Var. 9393	Var. 9450	Var. 9507	Var. 9564
	5-100	Var. 9223	Var. 9280	Var. 9337	Var. 9394	Var. 9451	Var. 9508	Var. 9565
	5-75	Var. 9224	Var. 9281	Var. 9338	Var. 9395	Var. 9452	Var. 9509	Var. 9566
	5-50	Var. 9225	Var. 9282	Var. 9339	Var. 9396	Var. 9453	Var. 9510	Var. 9567
	5-25	Var. 9226	Var. 9283	Var. 9340	Var. 9397	Var. 9454	Var. 9511	Var. 9568
	5-10	Var. 9227	Var. 9284	Var. 9341	Var. 9398	Var. 9455	Var. 9512	Var. 9569
	10-200	Var. 9228	Var. 9285	Var. 9342	Var. 9399	Var. 9456	Var. 9513	Var. 9570
	10-150	Var. 9229	Var. 9286	Var. 9343	Var. 9400	Var. 9457	Var. 9514	Var. 9571
	10-100	Var. 9230	Var. 9287	Var. 9344	Var. 9401	Var. 9458	Var. 9515	Var. 9572
	10-75	Var. 9231	Var. 9288	Var. 9345	Var. 9402	Var. 9459	Var. 9516	Var. 9573
	10-50	Var. 9232	Var. 9289	Var. 9346	Var. 9403	Var. 9460	Var. 9517	Var. 9574
	10-25	Var. 9233	Var. 9290	Var. 9347	Var. 9404	Var. 9461	Var. 9518	Var. 9575
	25-200	Var. 9234	Var. 9291	Var. 9348	Var. 9405	Var. 9462	Var. 9519	Var. 9576
	25-150	Var. 9235	Var. 9292	Var. 9349	Var. 9406	Var. 9463	Var. 9520	Var. 9577
	25-100	Var. 9236	Var. 9293	Var. 9350	Var. 9407	Var. 9464	Var. 9521	Var. 9578
	25-75	Var. 9237	Var. 9294	Var. 9351	Var. 9408	Var. 9465	Var. 9522	Var. 9579
	25-50	Var. 9238	Var. 9295	Var. 9352	Var. 9409	Var. 9466	Var. 9523	Var. 9580
	50-200	Var. 9239	Var. 9296	Var. 9353	Var. 9410	Var. 9467	Var. 9524	Var. 9581
	50-150	Var. 9240	Var. 9297	Var. 9354	Var. 9411	Var. 9468	Var. 9525	Var. 9582
	50-100	Var. 9241	Var. 9298	Var. 9355	Var. 9412	Var. 9469	Var. 9526	Var. 9583
	50-75	Var. 9242	Var. 9299	Var. 9356	Var. 9413	Var. 9470	Var. 9527	Var. 9584
	75-200	Var. 9243	Var. 9300	Var. 9357	Var. 9414	Var. 9471	Var. 9528	Var. 9585
	75-175	Var. 9244	Var. 9301	Var. 9358	Var. 9415	Var. 9472	Var. 9529	Var. 9586
	75-150	Var. 9245	Var. 9302	Var. 9359	Var. 9416	Var. 9473	Var. 9530	Var. 9587
	75-125	Var. 9246	Var. 9303	Var. 9360	Var. 9417	Var. 9474	Var. 9531	Var. 9588
	75-100	Var. 9247	Var. 9304	Var. 9361	Var. 9418	Var. 9475	Var. 9532	Var. 9589

TABLE 31-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	40-125	40-100	40-90	40-80	40-70	40-60	40-50	
100-200	Var. 9248	Var. 9305	Var. 9362	Var. 9419	Var. 9476	Var. 9533	Var. 9590	
100-175	Var. 9249	Var. 9306	Var. 9363	Var. 9420	Var. 9477	Var. 9534	Var. 9591	
100-150	Var. 9250	Var. 9307	Var. 9364	Var. 9421	Var. 9478	Var. 9535	Var. 9592	
100-125	Var. 9251	Var. 9308	Var. 9365	Var. 9422	Var. 9479	Var. 9536	Var. 9593	
125-200	Var. 9252	Var. 9309	Var. 9366	Var. 9423	Var. 9480	Var. 9537	Var. 9594	
125-175	Var. 9253	Var. 9310	Var. 9367	Var. 9424	Var. 9481	Var. 9538	Var. 9595	
125-150	Var. 9254	Var. 9311	Var. 9368	Var. 9425	Var. 9482	Var. 9539	Var. 9596	
150-200	Var. 9255	Var. 9312	Var. 9369	Var. 9426	Var. 9483	Var. 9540	Var. 9597	
150-200	Var. 9256	Var. 9313	Var. 9370	Var. 9427	Var. 9484	Var. 9541	Var. 9598	
175-200	Var. 9257	Var. 9314	Var. 9371	Var. 9428	Var. 9485	Var. 9542	Var. 9599	

Var. = Variation

TABLE 32

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.								
Specific Activity (mU/ μ g)								
	60-150	60-125	60-100	60-90	60-80	60-70		
Dosage (IU/kg rVWF:RCo activity)	0.5-200	Var. 9600	Var. 9657	Var. 9714	Var. 9771	Var. 9828	Var. 9885	
	0.5-150	Var. 9601	Var. 9658	Var. 9715	Var. 9772	Var. 9829	Var. 9886	
	0.5-100	Var. 9602	Var. 9659	Var. 9716	Var. 9773	Var. 9830	Var. 9887	
	0.5-75	Var. 9603	Var. 9660	Var. 9717	Var. 9774	Var. 9831	Var. 9888	
	0.5-50	Var. 9604	Var. 9661	Var. 9718	Var. 9775	Var. 9832	Var. 9889	
	0.5-25	Var. 9605	Var. 9662	Var. 9719	Var. 9776	Var. 9833	Var. 9890	
	0.5-10	Var. 9606	Var. 9663	Var. 9720	Var. 9777	Var. 9834	Var. 9891	
	0.5-5	Var. 9607	Var. 9664	Var. 9721	Var. 9778	Var. 9835	Var. 9892	
	0.5-2.5	Var. 9608	Var. 9665	Var. 9722	Var. 9779	Var. 9836	Var. 9893	
	0.5-1	Var. 9609	Var. 9666	Var. 9723	Var. 9780	Var. 9837	Var. 9894	
	2.5-200	Var. 9610	Var. 9667	Var. 9724	Var. 9781	Var. 9838	Var. 9895	
	2.5-150	Var. 9611	Var. 9668	Var. 9725	Var. 9782	Var. 9839	Var. 9896	
	2.5-100	Var. 9612	Var. 9669	Var. 9726	Var. 9783	Var. 9840	Var. 9897	
	2.5-75	Var. 9613	Var. 9670	Var. 9727	Var. 9784	Var. 9841	Var. 9898	
	2.5-50	Var. 9614	Var. 9671	Var. 9728	Var. 9785	Var. 9842	Var. 9899	
	2.5-25	Var. 9615	Var. 9672	Var. 9729	Var. 9786	Var. 9843	Var. 9900	
	2.5-10	Var. 9616	Var. 9673	Var. 9730	Var. 9787	Var. 9844	Var. 9901	
	2.5-5	Var. 9617	Var. 9674	Var. 9731	Var. 9788	Var. 9845	Var. 9902	
	5-200	Var. 9618	Var. 9675	Var. 9732	Var. 9789	Var. 9846	Var. 9903	
	5-175	Var. 9619	Var. 9676	Var. 9733	Var. 9790	Var. 9847	Var. 9904	
	5-150	Var. 9620	Var. 9677	Var. 9734	Var. 9791	Var. 9848	Var. 9905	
	5-125	Var. 9621	Var. 9678	Var. 9735	Var. 9792	Var. 9849	Var. 9906	
	5-100	Var. 9622	Var. 9679	Var. 9736	Var. 9793	Var. 9850	Var. 9907	
	5-75	Var. 9623	Var. 9680	Var. 9737	Var. 9794	Var. 9851	Var. 9908	
	5-50	Var. 9624	Var. 9681	Var. 9738	Var. 9795	Var. 9852	Var. 9909	
	5-25	Var. 9625	Var. 9682	Var. 9739	Var. 9796	Var. 9853	Var. 9910	
	5-10	Var. 9626	Var. 9683	Var. 9740	Var. 9797	Var. 9854	Var. 9911	
	10-200	Var. 9627	Var. 9684	Var. 9741	Var. 9798	Var. 9855	Var. 9912	
	10-150	Var. 9628	Var. 9685	Var. 9742	Var. 9799	Var. 9856	Var. 9913	
	10-100	Var. 9629	Var. 9686	Var. 9743	Var. 9800	Var. 9857	Var. 9914	
	10-75	Var. 9630	Var. 9687	Var. 9744	Var. 9801	Var. 9858	Var. 9915	
	10-50	Var. 9631	Var. 9688	Var. 9745	Var. 9802	Var. 9859	Var. 9916	
	10-25	Var. 9632	Var. 9689	Var. 9746	Var. 9803	Var. 9860	Var. 9917	
	25-200	Var. 9633	Var. 9690	Var. 9747	Var. 9804	Var. 9861	Var. 9918	
	25-150	Var. 9634	Var. 9691	Var. 9748	Var. 9805	Var. 9862	Var. 9919	
	25-100	Var. 9635	Var. 9692	Var. 9749	Var. 9806	Var. 9863	Var. 9920	
	25-75	Var. 9636	Var. 9693	Var. 9750	Var. 9807	Var. 9864	Var. 9921	
	25-50	Var. 9637	Var. 9694	Var. 9751	Var. 9808	Var. 9865	Var. 9922	
	50-200	Var. 9638	Var. 9695	Var. 9752	Var. 9809	Var. 9866	Var. 9923	
	50-150	Var. 9639	Var. 9696	Var. 9753	Var. 9810	Var. 9867	Var. 9924	
	50-100	Var. 9640	Var. 9697	Var. 9754	Var. 9811	Var. 9868	Var. 9925	
	50-75	Var. 9641	Var. 9698	Var. 9755	Var. 9812	Var. 9869	Var. 9926	
	75-200	Var. 9642	Var. 9699	Var. 9756	Var. 9813	Var. 9870	Var. 9927	
	75-175	Var. 9643	Var. 9700	Var. 9757	Var. 9814	Var. 9871	Var. 9928	
	75-150	Var. 9644	Var. 9701	Var. 9758	Var. 9815	Var. 9872	Var. 9929	
	75-125	Var. 9645	Var. 9702	Var. 9759	Var. 9816	Var. 9873	Var. 9930	
	75-100	Var. 9646	Var. 9703	Var. 9760	Var. 9817	Var. 9874	Var. 9931	
	100-200	Var. 9647	Var. 9704	Var. 9761	Var. 9818	Var. 9875	Var. 9932	
	100-175	Var. 9648	Var. 9705	Var. 9762	Var. 9819	Var. 9876	Var. 9933	

TABLE 32-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.							
Specific Activity (mU/ μ g)							
	60-150	60-125	60-100	60-90	60-80	60-70	
100-150	Var. 9649	Var. 9706	Var. 9763	Var. 9820	Var. 9877	Var. 9934	
100-125	Var. 9650	Var. 9707	Var. 9764	Var. 9821	Var. 9878	Var. 9935	
125-200	Var. 9651	Var. 9708	Var. 9765	Var. 9822	Var. 9879	Var. 9936	
125-175	Var. 9652	Var. 9709	Var. 9766	Var. 9823	Var. 9880	Var. 9937	
125-150	Var. 9653	Var. 9710	Var. 9767	Var. 9824	Var. 9881	Var. 9938	
150-200	Var. 9654	Var. 9711	Var. 9768	Var. 9825	Var. 9882	Var. 9939	
150-200	Var. 9655	Var. 9712	Var. 9769	Var. 9826	Var. 9883	Var. 9940	
175-200	Var. 9656	Var. 9713	Var. 9770	Var. 9827	Var. 9884	Var. 9941	

Var. = Variation

TABLE 33

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.							
Specific Activity (mU/ μ g)							
	70-150	70-125	70-100	70-90	70-80	80-150	
Dosage	0.5-200	Var. 9942	Var. 9999	Var. 10056	Var. 10113	Var. 10170	Var. 10227
(IU/kg	0.5-150	Var. 9943	Var. 10000	Var. 10057	Var. 10114	Var. 10171	Var. 10228
rVWF:	0.5-100	Var. 9944	Var. 10001	Var. 10058	Var. 10115	Var. 10172	Var. 10229
RCo	0.5-75	Var. 9945	Var. 10002	Var. 10059	Var. 10116	Var. 10173	Var. 10230
activity	0.5-50	Var. 9946	Var. 10003	Var. 10060	Var. 10117	Var. 10174	Var. 10231
	0.5-25	Var. 9947	Var. 10004	Var. 10061	Var. 10118	Var. 10175	Var. 10232
	0.5-10	Var. 9948	Var. 10005	Var. 10062	Var. 10119	Var. 10176	Var. 10233
	0.5-5	Var. 9949	Var. 10006	Var. 10063	Var. 10120	Var. 10177	Var. 10234
	0.5-2.5	Var. 9950	Var. 10007	Var. 10064	Var. 10121	Var. 10178	Var. 10235
	0.5-1	Var. 9951	Var. 10008	Var. 10065	Var. 10122	Var. 10179	Var. 10236
	2.5-200	Var. 9952	Var. 10009	Var. 10066	Var. 10123	Var. 10180	Var. 10237
	2.5-150	Var. 9953	Var. 10010	Var. 10067	Var. 10124	Var. 10181	Var. 10238
	2.5-100	Var. 9954	Var. 10011	Var. 10068	Var. 10125	Var. 10182	Var. 10239
	2.5-75	Var. 9955	Var. 10012	Var. 10069	Var. 10126	Var. 10183	Var. 10240
	2.5-50	Var. 9956	Var. 10013	Var. 10070	Var. 10127	Var. 10184	Var. 10241
	2.5-25	Var. 9957	Var. 10014	Var. 10071	Var. 10128	Var. 10185	Var. 10242
	2.5-10	Var. 9958	Var. 10015	Var. 10072	Var. 10129	Var. 10186	Var. 10243
	2.5-5	Var. 9959	Var. 10016	Var. 10073	Var. 10130	Var. 10187	Var. 10244
	5-200	Var. 9960	Var. 10017	Var. 10074	Var. 10131	Var. 10188	Var. 10245
	5-175	Var. 9961	Var. 10018	Var. 10075	Var. 10132	Var. 10189	Var. 10246
	5-150	Var. 9962	Var. 10019	Var. 10076	Var. 10133	Var. 10190	Var. 10247
	5-125	Var. 9963	Var. 10020	Var. 10077	Var. 10134	Var. 10191	Var. 10248
	5-100	Var. 9964	Var. 10021	Var. 10078	Var. 10135	Var. 10192	Var. 10249
	5-75	Var. 9965	Var. 10022	Var. 10079	Var. 10136	Var. 10193	Var. 10250
	5-50	Var. 9966	Var. 10023	Var. 10080	Var. 10137	Var. 10194	Var. 10251
	5-25	Var. 9967	Var. 10024	Var. 10081	Var. 10138	Var. 10195	Var. 10252
	5-10	Var. 9968	Var. 10025	Var. 10082	Var. 10139	Var. 10196	Var. 10253
	10-200	Var. 9969	Var. 10026	Var. 10083	Var. 10140	Var. 10197	Var. 10254
	10-150	Var. 9970	Var. 10027	Var. 10084	Var. 10141	Var. 10198	Var. 10255
	10-100	Var. 9971	Var. 10028	Var. 10085	Var. 10142	Var. 10199	Var. 10256
	10-75	Var. 9972	Var. 10029	Var. 10086	Var. 10143	Var. 10200	Var. 10257
	10-50	Var. 9973	Var. 10030	Var. 10087	Var. 10144	Var. 10201	Var. 10258
	10-25	Var. 9974	Var. 10031	Var. 10088	Var. 10145	Var. 10202	Var. 10259
	25-200	Var. 9975	Var. 10032	Var. 10089	Var. 10146	Var. 10203	Var. 10260
	25-150	Var. 9976	Var. 10033	Var. 10090	Var. 10147	Var. 10204	Var. 10261
	25-100	Var. 9977	Var. 10034	Var. 10091	Var. 10148	Var. 10205	Var. 10262
	25-75	Var. 9978	Var. 10035	Var. 10092	Var. 10149	Var. 10206	Var. 10263
	25-50	Var. 9979	Var. 10036	Var. 10093	Var. 10150	Var. 10207	Var. 10264
	50-200	Var. 9980	Var. 10037	Var. 10094	Var. 10151	Var. 10208	Var. 10265
	50-150	Var. 9981	Var. 10038	Var. 10095	Var. 10152	Var. 10209	Var. 10266
	50-100	Var. 9982	Var. 10039	Var. 10096	Var. 10153	Var. 10210	Var. 10267
	50-75	Var. 9983	Var. 10040	Var. 10097	Var. 10154	Var. 10211	Var. 10268
	75-200	Var. 9984	Var. 10041	Var. 10098	Var. 10155	Var. 10212	Var. 10269
	75-175	Var. 9985	Var. 10042	Var. 10099	Var. 10156	Var. 10213	Var. 10270
	75-150	Var. 9986	Var. 10043	Var. 10100	Var. 10157	Var. 10214	Var. 10271
	75-125	Var. 9987	Var. 10044	Var. 10101	Var. 10158	Var. 10215	Var. 10272
	75-100	Var. 9988	Var. 10045	Var. 10102	Var. 10159	Var. 10216	Var. 10273
	100-200	Var. 9989	Var. 10046	Var. 10103	Var. 10160	Var. 10217	Var. 10274
	100-175	Var. 9990	Var. 10047	Var. 10104	Var. 10161	Var. 10218	Var. 10275
	100-150	Var. 9991	Var. 10048	Var. 10105	Var. 10162	Var. 10219	Var. 10276
	100-125	Var. 9992	Var. 10049	Var. 10106	Var. 10163	Var. 10220	Var. 10277

TABLE 33-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.						
Specific Activity (mU/ μ g)						
	70-150	70-125	70-100	70-90	70-80	80-150
125-200	Var. 9993	Var. 10050	Var. 10107	Var. 10164	Var. 10221	Var. 10278
125-175	Var. 9994	Var. 10051	Var. 10108	Var. 10165	Var. 10222	Var. 10279
125-150	Var. 9995	Var. 10052	Var. 10109	Var. 10166	Var. 10223	Var. 10280
150-200	Var. 9996	Var. 10053	Var. 10110	Var. 10167	Var. 10224	Var. 10281
150-200	Var. 9997	Var. 10054	Var. 10111	Var. 10168	Var. 10225	Var. 10282
175-200	Var. 9998	Var. 10055	Var. 10112	Var. 10169	Var. 10226	Var. 10283

Var. = Variation

TABLE 34

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.							
Specific Activity (mU/ μ g)							
	80-125	80-100	80-90	90-150	90-125	90-100	
Dosage	0.5-200	Var. 10284	Var. 10341	Var. 10398	Var. 10455	Var. 10512	Var. 10569
(IU/kg rVWF:RCo	0.5-150	Var. 10285	Var. 10342	Var. 10399	Var. 10456	Var. 10513	Var. 10570
activity)	0.5-100	Var. 10286	Var. 10343	Var. 10400	Var. 10457	Var. 10514	Var. 10571
	0.5-75	Var. 10287	Var. 10344	Var. 10401	Var. 10458	Var. 10515	Var. 10572
	0.5-50	Var. 10288	Var. 10345	Var. 10402	Var. 10459	Var. 10516	Var. 10573
	0.5-25	Var. 10289	Var. 10346	Var. 10403	Var. 10460	Var. 10517	Var. 10574
	0.5-10	Var. 10290	Var. 10347	Var. 10404	Var. 10461	Var. 10518	Var. 10575
	0.5-5	Var. 10291	Var. 10348	Var. 10405	Var. 10462	Var. 10519	Var. 10576
	0.5-2.5	Var. 10292	Var. 10349	Var. 10406	Var. 10463	Var. 10520	Var. 10577
	0.5-1	Var. 10293	Var. 10350	Var. 10407	Var. 10464	Var. 10521	Var. 10578
	2.5-200	Var. 10294	Var. 10351	Var. 10408	Var. 10465	Var. 10522	Var. 10579
	2.5-150	Var. 10295	Var. 10352	Var. 10409	Var. 10466	Var. 10523	Var. 10580
	2.5-100	Var. 10296	Var. 10353	Var. 10410	Var. 10467	Var. 10524	Var. 10581
	2.5-75	Var. 10297	Var. 10354	Var. 10411	Var. 10468	Var. 10525	Var. 10582
	2.5-50	Var. 10298	Var. 10355	Var. 10412	Var. 10469	Var. 10526	Var. 10583
	2.5-25	Var. 10299	Var. 10356	Var. 10413	Var. 10470	Var. 10527	Var. 10584
	2.5-10	Var. 10300	Var. 10357	Var. 10414	Var. 10471	Var. 10528	Var. 10585
	23-5	Var. 10301	Var. 10358	Var. 10415	Var. 10472	Var. 10529	Var. 10586
	5-200	Var. 10302	Var. 10359	Var. 10416	Var. 10473	Var. 10530	Var. 10587
	5-175	Var. 10303	Var. 10360	Var. 10417	Var. 10474	Var. 10531	Var. 10588
	5-150	Var. 10304	Var. 10361	Var. 10418	Var. 10475	Var. 10532	Var. 10589
	5-125	Var. 10305	Var. 10362	Var. 10419	Var. 10476	Var. 10533	Var. 10590
	5-100	Var. 10306	Var. 10363	Var. 10420	Var. 10477	Var. 10534	Var. 10591
	5-75	Var. 10307	Var. 10364	Var. 10421	Var. 10478	Var. 10535	Var. 10592
	5-50	Var. 10308	Var. 10365	Var. 10422	Var. 10479	Var. 10536	Var. 10593
	5-25	Var. 10309	Var. 10366	Var. 10423	Var. 10480	Var. 10537	Var. 10594
	5-10	Var. 10310	Var. 10367	Var. 10424	Var. 10481	Var. 10538	Var. 10595
	10-200	Var. 10311	Var. 10368	Var. 10425	Var. 10482	Var. 10539	Var. 10596
	10-150	Var. 10312	Var. 10369	Var. 10426	Var. 10483	Var. 10540	Var. 10597
	10-100	Var. 10313	Var. 10370	Var. 10427	Var. 10484	Var. 10541	Var. 10598
	10-75	Var. 10314	Var. 10371	Var. 10428	Var. 10485	Var. 10542	Var. 10599
	10-50	Var. 10315	Var. 10372	Var. 10429	Var. 10486	Var. 10543	Var. 10600
	10-25	Var. 10316	Var. 10373	Var. 10430	Var. 10487	Var. 10544	Var. 10601
	25-200	Var. 10317	Var. 10374	Var. 10431	Var. 10488	Var. 10545	Var. 10602
	25-150	Var. 10318	Var. 10375	Var. 10432	Var. 10489	Var. 10546	Var. 10603
	25-100	Var. 10319	Var. 10376	Var. 10433	Var. 10490	Var. 10547	Var. 10604
	25-75	Var. 10320	Var. 10377	Var. 10434	Var. 10491	Var. 10548	Var. 10605
	25-50	Var. 10321	Var. 10378	Var. 10435	Var. 10492	Var. 10549	Var. 10606
	50-200	Var. 10322	Var. 10379	Var. 10436	Var. 10493	Var. 10550	Var. 10607
	50-150	Var. 10323	Var. 10380	Var. 10437	Var. 10494	Var. 10551	Var. 10608
	50-100	Var. 10324	Var. 10381	Var. 10438	Var. 10495	Var. 10552	Var. 10609
	50-75	Var. 10325	Var. 10382	Var. 10439	Var. 10496	Var. 10553	Var. 10610
	75-200	Var. 10326	Var. 10383	Var. 10440	Var. 10497	Var. 10554	Var. 10611
	75-175	Var. 10327	Var. 10384	Var. 10441	Var. 10498	Var. 10555	Var. 10612
	75-150	Var. 10328	Var. 10385	Var. 10442	Var. 10499	Var. 10556	Var. 10613
	75-125	Var. 10329	Var. 10386	Var. 10443	Var. 10500	Var. 10557	Var. 10614
	75-100	Var. 10330	Var. 10387	Var. 10444	Var. 10501	Var. 10558	Var. 10615
	100-200	Var. 10331	Var. 10388	Var. 10445	Var. 10502	Var. 10559	Var. 10616
	100-175	Var. 10332	Var. 10389	Var. 10446	Var. 10503	Var. 10560	Var. 10617
	100-150	Var. 10333	Var. 10390	Var. 10447	Var. 10504	Var. 10561	Var. 10618
	100-125	Var. 10334	Var. 10391	Var. 10448	Var. 10505	Var. 10562	Var. 10619
	125-200	Var. 10335	Var. 10392	Var. 10449	Var. 10506	Var. 10563	Var. 10620
	125-175	Var. 10336	Var. 10393	Var. 10450	Var. 10507	Var. 10564	Var. 10621

TABLE 34-continued

Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.							
Specific Activity (mU/ μ g)							
	80-125	80-100	80-90	90-150	90-125	90-100	
125-150	Var. 10337	Var. 10394	Var. 10451	Var. 10508	Var. 10565	Var. 10622	
150-200	Var. 10338	Var. 10395	Var. 10452	Var. 10509	Var. 10566	Var. 10623	
150-200	Var. 10339	Var. 10396	Var. 10453	Var. 10510	Var. 10567	Var. 10624	
175-200	Var. 10340	Var. 10397	Var. 10454	Var. 10511	Var. 10568	Var. 10625	

Var. = Variation

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF

multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 18 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 24 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 30 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

Administration of rVWF/rFVIII

In one aspect, the present disclosure provides method for treating Von Willebrand Disease (VWD) or Hemophilia A in a subject in need thereof, which includes administering a composition of recombinant Von Willebrand Factor (rVWF) and recombinant FVIII (rFVIII) such that Factor VIII (FVIII) stability is increased, as compared to FVIII half-life in a subject administered a composition of plasma derived Von Willebrand Factor (pdVWF). In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher VWF specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 10%, 20%, 30%, 2 hr, 4 hr, 6 hr, or by an amount selected from variations 1300 to 1643 found in Table 9, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 10% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 20% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF

multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 30% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a

multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 10 IU/kg to 40 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the composition contains from 20 IU/kg to 30 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 25 IU/kg to 75 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the composition contains from 40 IU/kg to 60 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 75 IU/kg to 125 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the composition contains from 75 IU/kg to 100 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the subject is administered a dose of rVWF selected from variations 2141 to 2338 in Table 12, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the

half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of from 40 mU/ μ g to 60 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of at least 60 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of at least 80 mU/ μ g, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity selected from variations 1 to 133 found in Table 1, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in Table 20 to Table 27. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the dose of rVWF and

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCO) in the composition is from 4:1-3:2, and wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in Table 3 to Table 5. In a specific

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in Table 13 to Table 19.

further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in Table 11, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in Table 28 to Table 34. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the example herein below. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV), *Using Antibodies: A Laboratory Manual*, *Cells: A Laboratory Manual*, *PCR Primer: A Laboratory Manual*, and *Molecular Cloning: A Laboratory Manual* (all from Cold Spring Harbor Laboratory Press), Stryer, L. (1995) *Biochemistry* (4th Ed.) Freeman, Highly stabilized York, Gait, "Oligonucleotide Synthesis: A Practical Approach" 1984, IRL Press, London, Nelson and Cox (2000), *Lehninger, Principles of Biochemistry* 3rd Ed., W. H. Freeman Pub., Highly stabilized York, N.Y. and Berg et al. (2002) *Biochemistry*, 5th Ed., W. H. Freeman Pub., Highly stabilized York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

Note that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymerase" refers to one agent or mixtures of such agents, and reference to "the method"

includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing devices, compositions, formulations and methodologies which are described in the publication and which might be used in connection with the presently described invention.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

In the above description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

Although the present invention is described primarily with reference to specific embodiments, it is also envisioned that other embodiments will become apparent to those skilled in the art upon reading the present disclosure, and it is intended that such embodiments be contained within the present inventive methods.

EXAMPLES

Example 1

Study of rVWF:rFVIII Co-Administration.

The immediate tolerability and safety after single doses of rVWF:rFVIII at 2 IU/kg, 7.5 IU/kg, 20 IU/kg and 50 IU/kg VWF:RCo was assessed as a primary endpoint of the study. Secondary endpoints included PK for VWF:RCo, VWF:CB, VWF:Ag, FVIII and multimeric composition of the VWF. An additional secondary endpoint was a PK comparison with pdVWF/pdFVIII [Cohort 4 (50 IU/kg VWF:RCo)]. See FIG. 1 for a schematic illustration of the study design.

Recombinant human Von Willebrand Factor (rVWF) was expressed in CHO cells. Propeptide removal was mediated in vitro through exposure of the pro-VWF to recombinant Furin. Fully glycosylated/ABO blood groups glycans were absent. The recombinant VWF has higher specific activity than plasma-derived VWF (pdVWF) and offers the therapeutic flexibility of dosing with or without rFVIII. The rVWF used in this study was not exposed to ADAMTS13, resulting in the presence of ultra-large VWF multimers and intact VWF subunits. ADAMTS13 results in subunit cleavage at TYR¹⁶⁰⁵-MET¹⁶⁰⁶.

VWF:RCo PK/VWF multimer kinetics showed highly similar PK for VWF:RCo (VWF activity) between rVWF and Humate P (FIG. 2A). Humate P is human derived medium purity Factor VIII concentrates complexed to VWF. A surrogate marker was used for efficacy and dosing recommendations. The data in FIG. 2A show that rVWF shows similar

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activity to that of plasma derived VWF. Progressive loss of high molecular weight rVWF was seen upon exposure to ADAMTS13 (FIG. 2B), showing that rVWF is present in high molecular weight multimers prior to the ADAMTS13 exposure.

Higher FVIII levels were observed in rVWF patients as compared to Humate (FIG. 3). These data show that rVWF stabilizes endogenous FVIII in vivo. There was a difference in effects seen with different VWF:FVIII ratios (1.3:1 vs. ~2.1 VWF:FVIII). These different ratios suggest that less rVWF can be used to stabilize FVIII than is needed when using plasma derived VWF. The study design provided a flexibility of re-dosing with rVWF alone (no rFVIII) after the initial dose.

Ultra-large molecular weight multimers are present with rVWF—these ultra-large molecular weight multimers rapidly disappear following infusion. ADAMTS13 mediated cleavage fragments were seen in all subjects. The pharmacokinetic profile of VWF:RCo was similar to that of pdVWF. There was sustained stabilization of endogenous FVIII with rVWF which was comparable to that observed with pdVWF. The adverse drug reaction profile with rVWF was similar to that of pdVWF/pdFVIII, and all related adverse events (AEs) were mild.

The overall safety and pharmacokinetic profile suggests that rVWF can be used for the treatment and preventing of bleeding episodes at doses comparable to pdVWF/pdFVIII, while enhancing the levels of FVIII as compared to the effect from the use of pdVWF. Without being limited by theory, it is possible that the high proportion of ultra-large multimers (decamers or higher) in the population of rVWF leads to the enhanced stabilization of FVIII seen with rVWF as compared to that by plasma derived VWF.

Example 2

In-Human Study Evaluating Pharmacokinetics Demonstrating Safety and Tolerability in Severe Von Willebrand Disease (VWD).

This study compared the effects of pdVWF and rVWF in patients with type 3 VWD or severe Type 1 VWD.

The pdVWF used in this study was synthesized in endothelial cells and megakaryocytes. Post-translational modification of propeptide removal occurred intracellularly during passage of the protein to the Golgi and post-Golgi compartments. Glycosylation/ABO blood group glycans were present. The pdVWF consisted of VWF subunits that had been exposed to plasma ADAMTS13. There were no ultra-large VWF multimers in the pdVWF population and subunits were cleaved at TYR¹⁶⁰⁵-MET¹⁶⁰⁶. pdVWF concentrates contained other proteins, including ADAMTS13 and hemagglutinins.

The rVWF used in this study was expressed in CHO cells. Propeptide removal was mediated in vitro through exposure of the pro-VWF to recombinant Furin. Fully glycosylated/ABO blood group glycans were absent. The rVWF was not exposed to ADAMTS13. The subunits of the rVWF were intact and ultra-large VWF multimers were present. Subunit cleavage did occur upon ADAMTS13 exposure. The rVWF showed higher specific activity than pdVWF.

The inclusion criteria for this study were:

- Type 3 VWD (VWF:Ag≤3 IU/dL)
- Severe Type 1 VWD (VWF:RCo≤10 IU/dL and FVIII:C<20 IU/dL
- 18 to 60 years of age
- Previous coagulation factor replacement therapy (≥25 ED)
- Non-bleeding state

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The exclusion criteria for this study were:

- Other coagulation disorders
- History of VWF and/or FVIII inhibitors
- Cardiovascular disease
- Medical history of thromboembolic event
- Medical history of other immunological disorders

The immediate tolerability and safety after single doses of rVWF:rFVIII at 2 IU/kg, 7.5 IU/kg, 20 IU/kg and 50 IU/kg VWF:RCo was assessed as a primary endpoint of this study.

Secondary endpoints included PK for VWF:RCo, VWF:CB, VWF:Ag, FVIII and multimeric composition of the VWF. An additional secondary endpoint was a PK comparison with pdVWF/pdFVIII [Cohort 4 (50 IU/kg VWF:RCo)]. Patient demographics for this study are shown in FIG. 4. Pharmacokinetic analysis of Cohort 4A (Type 3 VWD) VWF:RCo/VWF:Ag is shown in FIG. 5. These data show that the total activities of rVWF were comparable to those of pdVWF. Progressive loss of high molecular weight rVWF was seen upon exposure to ADAMTS13 (FIG. 6). Further pharmacokinetic analysis of Cohort 4A (Type 3 VWD) FVIII:C is shown in FIG. 7. The data in FIG. 7 suggests that rVWF was more effective at stabilizing the in vivo activity of FVIII than pdVWF, resulting in increased FVIII procoagulant activity after treatment with rVWF/rVWF as compared to treatment with pdVWF/pdFVIII.

Ultra-large molecular weight multimers were present in rVWF and rapidly disappeared following infusion. ADAMTS13 mediated cleavage fragments were seen in all subjects. The pharmacokinetic profile of VWF:RCo was similar to that of pdVWF. There was sustained stabilization of endogenous FVIII that was comparable to that observed with pdVWF. The adverse drug reaction profile was similar to that of pdVWF/pdFVIII, and all related adverse events were mild.

The overall safety and pharmacokinetic profile suggests that rVWF can be used for the treatment and preventing of bleeding episodes at doses comparable to pdVWF/pdFVIII.

Example 3

Clinical Study of rVWF:rFVIII Complex.

This study was a pharmacokinetics, immediate safety and tolerability study in congenital von Willebrand disease Type 3. FIG. 9 shows the rVWF PK parameters for three patients in the study.

FIG. 10 shows PK data for Patient 1. There was a good correlation between VWF:RCo and VWF:CBA. Activities were measurable up to 12 hours (both were below the limit of quantification at 24 hours). VWF:Ag was still measurable at 96 hours. Endogenous FVIII activity increased to a maximum of 0.13 IU/mL.

FIG. 11 shows PK data in Patient 2. As with Patient 1, there was a good correlation between VWF:RCo and VWF:CBA. Both activities were measurable (albeit at the limit of quantification) up to 12 hours. VWF:Ag was still measurable at 72 hours (the 96 hour sample was not tested). Endogenous FVIII activity increased to a maximum of 0.18 IU/mL for this patient.

FIG. 12 shows PK data in Patient 3. VWF:RCo activity was measurable up to 24 hours (albeit at the limit of quantification), while VWF:CBA was below LoQ at 24 hours. VWF:Ag was still measurable up to 48 hours. Endogenous FVIII activity increased to a maximum of 0.13 IU/mL for this patient.

FIG. 13 shows data comparing the VWF parameters and FVIII activity for the three patients. There was a good correlation seen in all three patients for all parameters tested (VWF:RCo, VWF:CBA, VWF:Ag, and FVII:Chr activity).

rVWF had ~100% recovery in all patients. The three patients showed slightly different rVWF PK. For VWF antigen, there was a maximum 0.06 IU/ml 30 minutes after application of 2 IU VWF:RCo/kg followed by a steady decline. For FVIII activity, the baseline FVIII activity increased to approximately 0.1 IU/ml 15 minutes after application of rVWF+rFVIII. Thereafter, activity further increased to 0.16 IU/ml, reached a plateau at 3-6 hours that stayed up to 28 hours followed by a steady decline. The delayed increase in FVIII indicates that the secondary rise was induced by rVWF.

Example 4

rVWF Study-FVII PK Assessment and TA Assessment.

FIG. 14 shows data for FVIII activity across all cohorts. FIG. 15 shows data from Cohort 1 (2 IU/kg VWF:RCo/1.5 IU/kg FVIII). There was good correlation for all three patients in this cohort for all parameters tested.

FIG. 15 shows data from Cohort 2 (7.5 IU/kg VWF:RCo/5.8 IU/kg FVIII). FIG. 16 shows the pharmacokinetics data for this cohort for FVIII:C.

FIG. 17 shows data for Cohort 3 (20 IU/kg VWF:RCo/15.4 IU/kg FVIII). These data show a comparison of plasma parameters for VWF and FVIII. FIG. 18 shows the pharmacokinetics data for this cohort for FVIII:C.

FIG. 19 shows data for Cohort 4 (50 IU/kg VWF:RCo). FVIII dosing was 38.5 IU/kg rFVIII or 25 IU/kg pdFVIII. These data show that the parameters for rVWF are similar to those for pdVWF (Haemate), but that rVWF is more effective at stabilizing FVIII activity, resulting in an increase seen in FVIII activity as compared to that seen with pdVWF. FIG. 20 shows a summary of pharmacokinetics data for this cohort for FVIII:C. As can be seen in these data, the median and mean $T_{1/2}$ was increased for rVWF/FVIII as compared to pdVWF/FVIII, suggesting that rVWF is more effective at stabilizing in vivo FVIII than is pdVWF resulting in increased half-life.

Example 5

Clinical Study of rVWF Effect on rFVIII Half-Life in the Treatment of Hemophilia A.

This study evaluates the immediate tolerability and safety of rVWF after single doses of 50 IU/kg rFVIII (Advate) alone or in combination with rVWF at 10 or 50 IU/kg von Willebrand Factor:Ristocetin cofactor activity (VWF:RCo). This study also evaluates the pharmacokinetics after single doses of 50 IU/kg rFVIII (Advate) alone or in combination with rVWF at 10 or 50 IU/kg (VWF:RCo).

The population for the study is selected using the following criteria:

Inclusion Criteria:

Severe Hemophilia A (FVIII:C<1 IU/dL)

18 to 60 years of age

Previous coagulation factor replacement therapy (>150 ED)

Non-bleeding state

Exclusion Criteria:

Other coagulation disorders

History of VWF and/or FVIII inhibitors

Cardiovascular disease

Medical history of thromboembolic event

Medical history of other immunological disorders (exceptions)

Subject participation is for 16 weeks with an overall study duration of 7 months.

The design of the study is a multicenter, uncontrolled, non randomized, open-label clinical study to assess safety, im-

mediate tolerability and pharmacokinetics of rFVIII:rVWF in subjects with hereditary severe hemophilia A (FVIII:C<1%).

Each subject (N=14) participating in the triple-period PK analysis receives in a non randomized fashion 50 IU/kg rFVIII (Advate) with no, 10 IU/kg VWF:RCo, or 50 IU/kg VWF:RCo rVWF, and is expected to participate for approximately 16 weeks.

The intra-individual pharmacokinetics are spaced at 5-14 days apart to ensure a "wash-out" period of at least 5 days and a timely completion of the study. Safety analyses are performed separately once 6 subjects have been dosed with 10 IU/KG VWF:RCo rVWF and once 6 subjects have been dosed with 50 IU/KG VWF:RCo rVWF.

Subjects should not have received cryoprecipitate, fresh frozen plasma or other drugs interfering with VWF or FVIII PK for at least 5 days before either of the infusions.

Dosage of rVWF is escalated when immediate tolerability and safety are demonstrated after a minimum of 6 subjects treated with 10 IU VWF:RCo rVWF. The effects of the investigational product on vital signs, hematology, and clinical chemistry parameters will determine short-term safety.

Samples for the determination of levels of FVIII activity (FVIII:C), VWF antigen (VWF:Ag), VWF activity (VWF:RCo), VWF:CB, (and VWF multimer distribution) are taken pre-infusion (within 30 minutes prior to the start of the infusion) and after the end of the infusion at 15 minutes (± 5 minutes), 30 minutes (± 5 minutes), 1 hour (± 5 minutes), 3 hours (± 10 minutes), 6 hours (± 10 minutes), 9 hours (± 15 minutes), 24 hours (± 2 hours) and 48 hours (± 2 hours), 72 hours (± 2 hours), 96 hours (± 2 hours), and 120 hours (± 2 hours) (or at least every 24 hours thereafter until FVIII drops below <1%). FVIII activity is determined using both the chromogenic and one-stage a PTT-based assay methods performed at the local and central laboratory.

The effects of each infusion on vital signs and other symptoms indicative of an adverse event (AE), hematology, and clinical chemistry parameters are used as indicators of short-term safety. Vital signs, clinical chemistry, and hematology parameters are assessed pre-infusion and until 120 hours post-infusion. The occurrence of AEs are continuously monitored for up to 2 hours post-infusion (rVWF treated subjects) and at various time points during the follow-up period.

The presence of inhibitors to FVIII and VWF are assessed before investigational product infusion and at the study completion visit.

If at any time a serious AE related to the investigational product occurs, an independent data monitoring committee (DMC) will advise whether to continue the study.

Pharmacokinetic primary endpoints for the study include: $AUC_{0-\infty}/Dose$ (area under the plasma concentration/time curve from time 0 to infinity); $AUC_{0-96h}/Dose$ (area under the plasma concentration/time curve from time 0 to 96 hours); mean residence time (MRT); clearance (CL); $T_{1/2}$ (elimination phase half-life); Volume of distribution at steady state (V_{ss}) of VWF:RCo, VWF:Ag, VWF:CB, and FVIII.

Analysis for pharmacokinetic primary endpoints include $AUC_{0-96h}/Dose$, $AUC_{0-\infty}/Dose$, MRT, CL, $T_{1/2}$ and V_{ss} summarized per treatment group (50 IU/kg rFVIII (Advate) alone, 50 IU/kg rFVIII (Advate) premixed with rVWF at 10 IU/kg VWF:RCo, 50 IU/kg rFVIII (Advate) premixed with rVWF at 50 IU/kg VWF:RCo) by median and two-sided 95% CIs for the median, mean, standard deviation, coefficient of variation and geometric mean. Descriptive statistics (medians and ranges) are used to summarize VWF:RCo, VWF:Ag, VWF:CB and FVIII levels over time.

Safety primary endpoint includes: occurrence of treatment related AEs. Analysis of the safety primary endpoint includes

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the number and percentage of subjects who experience a treatment related AE. The number and rate of treatment related AEs are tabulated.

Pharmacokinetic secondary endpoints include: In vivo recovery (IVR) and incremental recovery (IR) of FVIII, VWF:RCo, VWF:Ag and VWF:CB. Analysis of pharmacokinetic secondary endpoints includes determining IVR and IR of FVIII, VWF:RCo, VWF:Ag and VWF:CB by subject and summarizing by medians and ranges.

Safety secondary endpoints include: development of inhibitory and total binding anti-VWF antibodies, development of inhibitory antibodies to FVIII, development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin, occurrence of thrombotic events.

Safety secondary endpoints are analyzed by tabulating the number of subjects who experience an SAE and the number of SAEs. In addition, the number of subjects who experience a treatment related AE and the number and rate of treatment related AEs are subcategorized for thrombotic events, inhibitory and total binding anti-VWF antibodies, inhibitory antibodies to FVIII, antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

A listing of all AEs are presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date and medication or non-drug therapy to treat the AE. An overview table for AEs are provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to treatment. An additional summary table presents the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to treatment.

No formal sample size calculation has been conducted for this study.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

What is claimed is:

1. A method for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof, the method comprising: intravenously administering to the subject a composition comprising recombinant Von Willebrand Factor (rVWF) wherein endogenous Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein the rVWF is not modified with a water soluble polymer, wherein the composition is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, and wherein the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, and the higher order rVWF multimers are stable for at least 3 hours post-administration.

2. The method of claim 1, wherein the method comprises co-administering to the subject said composition comprising recombinant Von Willebrand Factor (rVWF) and a composition comprising recombinant Factor VIII (rFVIII).

3. The method of claim 2, wherein the rVWF and rFVIII are administered together in a single composition.

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4. The method according to claim 1, wherein the subject is administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose.

5. The method of claim 4, wherein the subject is administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose.

6. The method of claim 4, wherein the subject is administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose.

7. The method of claim 4, wherein the subject is administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

8. The method according to claim 1, wherein the rVWF is matured in vitro by treatment with Furin.

9. The method according to claim 1, wherein the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture).

10. The method according to claim 2, wherein the rFVIII and rVWF are produced through expression in the same cell culture.

11. The method according to claim 1, wherein the subject is administered rVWF no more than once every other day.

12. The method of claim 11, wherein the subject is administered rVWF no more than twice a week.

13. The method according claim 1, wherein the Factor VIII half-life is extended by at least 5 hours.

14. The method of claim 13, wherein the Factor VIII half-life is extended by at least 12 hours.

15. The method of claim 13, wherein the Factor VIII half-life is extended by at least 24 hours.

16. The method of claim 13, wherein the Factor VIII half-life is extended by at least 36 hours.

17. The method of claim 13, wherein the Factor VIII half-life is extended by at least 48 or 72 hours.

18. The method of claim 2, wherein the ratio of procoagulant activity (IU FVIII:C) of the administered FVIII to Ristocetin cofactor activity (IU rVWF:RCo) of the administered rVWF is between 2:1 and 1:4.

19. The method of claim 18, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) is between 3:2 and 1:3.

20. The method of claim 18, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) is between 1:1 and 1:2.

21. The method of claim 18, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) is about 3:4.

22. The method of claim 1, wherein the rVWF has a specific activity of about 20-150 mU/ μ g.

23. The method of claim 1, wherein the high molecular weight VWF multimer composition comprises at least 30% VWF decamers or higher order multimers.

24. The method of claim 1, wherein the high molecular weight VWF multimer composition comprises at least 40% VWF decamers or higher order multimers.

25. The method of claim 1, wherein the high molecular weight VWF multimer composition comprises at least 50% VWF decamers or higher order multimers.

26. The method of claim 1, wherein the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers.

27. The method of claim 1, wherein the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

28. A method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject a composition comprising

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recombinant Von Willebrand Factor (rVWF) wherein Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is about 20-150 mU/g; (b) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor; and (c) the rVWF is not modified with a water soluble polymer; and (d) the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, wherein the higher order rVWF multimers are stable for at least 3 hours post-administration.

29. A method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject a composition comprising recombinant Von Willebrand Factor (rVWF) wherein Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the composition is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher

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order multimers, (b) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is at least about 20-150 mU/g; (c) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor; and (d) the rVWF is not modified with a water soluble polymer; and (e) the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, wherein the higher order rVWF multimers are stable for at least 3 hours post-administration.

30. The method of claim **1, 28** or **29**, wherein the method is a method for treating Von Willebrand Disease Type 3.

31. The method of claim **1, 28** or **29**, wherein the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

32. The method of claim **1, 28** or **29** wherein said water soluble polymer is PEG.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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APPLICATION NO. : 13/493926
DATED : March 1, 2016
INVENTOR(S) : Friedrich Scheifflinger et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Claim 28, column 137, line 6: replace “20-150 mU/g” with “20-150 mU/μg”

Claim 28, column 137, line 8: delete “and”

Claim 29, column 138, line 3: replace “20-150 mU/g” with “20-150 mU/μg”

Claim 29, column 138, line 6: delete “and”

Signed and Sealed this
Twenty-third Day of August, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office